COMPARISON OF THIAMINE STATUS IN TYPE II DIABETES MELLITUS WITH AND WITHOUT LOWER EXTREMITY AMPUTATIONS: A PROSPECTIVE CASE CONTROL STUDY

A DISSERTATION SUBMITTED IN PARTIAL FULFULMENT OF THE REQUIREMENT FOR THE M.S. DEGREE (GENERAL SURGERY) EXAMINATION OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, MAY 2018

DECLARATION

I hereby declare that this dissertation titled **'Comparison Of Thiamine Status In Type II Diabetes Mellitus With And Without Lower Extremity Amputations: A Prospective Case Control Study'** was prepared by me in partial fulfilment of requirement of the regulations for the award of degree MS General Surgery of The Tamil Nadu Dr. M. G. R. University, Chennai. This has not formed the basis for the award of any degree to me before and I have not submitted this to any other university previously.

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CERTIFICATE

This is to certify that the dissertation entitled '**Comparison Of Thiamine Status In Type II Diabetes Mellitus With And Without Lower Extremity Amputations: A Prospective Case Control Study'** is a bonafide work of **Dr. Binoy Abraham**, towards the M. S. Branch (General Surgery) Degree Examination of the Tamil Nadu Dr. M. G. R. University, Chennai, to be conducted in May 2018.

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Abstract

Title: Comparison of thiamine status in type II diabetes mellitus with and without lower extremity amputations: A prospective case control study

Background: Diabetes Mellitus is quickly gaining the status of an epidemic in our country. The complications arising out of diabetes are one of the commonest problems encountered in the surgical outpatient clinics and the wards. Diabetic neuropathy along with microangiopathy predisposes the individual to development of diabetic ulcers which are treated with debridements or minor/major amputations depending upon the extent and severity of the lesion. Thiamine is a water soluble vitamin which takes part in the carbohydrate metabolism and is found to be deficient in chronic hyperglycaemic states. Thiamine and its synthetic derivatives have been shown to accelerate healing of ischemic diabetic limbs in animal models. Hence studies are required to determine and establish a correlation of diabetic patients undergoing lower extremity amputations and their thiamine levels.

Aim: To assess the thiamine levels of patients undergoing lower limb amputations due to uncontrolled diabetes mellitus type II

Study Design: Hospital based prospective case-control study

Materials and Methods: A hospital based prospective case control study was done among the patients in the wards of the general surgical units. The cases were the patients with diabetes mellitus, who underwent lower extremity amputations. The controls were the patients in the wards of the general surgical units with diabetes mellitus who were otherwise healthy and did not undergo a lower extremity amputation. A one-on-one interview was conducted using a questionnaire detailing the patient demographics, anthropometrics and neurological examination. A blood sample was collected, under standard precautions, for the measurement of Erythrocyte Transketolase Activity (ETKA), and the value was recorded in

the data collection sheet. The routine investigations done for diabetic work-up were collected from the hospital medical records system and recorded on the data collection sheet. The normal range of Transketolase activity was deduced from the control arm of the study.

Conclusion: The mean erythrocyte transketolase levels measured among the cases were lower than that for the control group but the difference was not statistically significant. Low thiamine levels were identified by using the mean value of the control arm as the lower limit of normal erythrocyte transketolase level. Using this value, sixty two percent of the cases were identified to have low thiamine levels. The low thiamine levels did not show any significant association with age, gender, body mass index or mode of diabetic treatment.

The low thiamine levels were also compared to markers of glycaemic control and level of neuropathy among the cases. However, there was no significant correlation between the low thiamine levels and HbA1c, urinary micro-albumin and modified neuropathy disability score. Interestingly, the median neuropathy score among the cases (NDS=8) was significantly higher than that in the control arm (NDS=4). This was an important finding since a score of six or more was predictive of foot ulceration and subsequent risk of amputation, in the precious limb of the patients who had already undergone amputations of the contra-lateral limbs. Also the median urinary micro-albumin among the cases (urine micro-albumin=70.5mg/mg of creatinine) was significantly higher than that among the controls (urine micro-albumin=17mg/mg of creatinine). The prevalence of abnormal urinary micro-albumin, suggestive of incipient diabetic nephropathy, was significantly high among cases (75%) as compared to the controls (33.3%).

In view of the above, it is imperative that further role of thiamine should be investigated to establish a correlation between thiamine deficiency and complications of diabetes mellitus.

Keywords: Diabetes mellitus, neuropathy, amputation, angiopathy, thiamine, benfotiamine.

Anti-Plagiarism Certificate

This is to certify that this dissertation work titled - "Comparison of thiamine status in type II Diabetes Mellitus with and without lower extremity amputations: A prospective case control study" of the candidate Dr. Binoy Abraham with registration Number 221511451has submitted his dissertation for verification and I have personally verified the Urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains the introduction to conclusion pages and the analysis shows 2 percentage of plagiarism in the dissertation.

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INTRODUCTION

Introduction

Diabetes Mellitus is one of the commonest illnesses that we come across in our outpatient clinics and the surgical wards. The complications of uncontrolled diabetes are a cause of significant morbidity and mortality in our daily practice.

Diabetes is rapidly gaining the status of an epidemic in India with more than 62 million individuals currently diagnosed with the illness(1). At present estimates, the prevalence of diabetes will exceed more than 350 million worldwide, with the maximum increase in India(2). In our country, the aetiology of diabetes is multifactorial and includes genetic factors coupled with environmental influences such as obesity associated with rising living standards, steady urban migration, and lifestyle changes(3). A study done by Indian Council of Medical Research shows that Tamil Nadu has the second highest prevalence of diabetes in our country with 4.8 million diagnosed cases(4) .Among individuals with diabetes, glycaemic control worsens with longer duration of the disease(5), with neuropathy being the most common complication(6). Poor glycaemic control is responsible for the development of diabetic myonecrosis (7) and muscle infarction(8). A combination of the afore-mentioned complications, results in development of ulcers on the lower extremities and subsequent superficial and deep soft tissue infections leading to major and minor amputations.

Thiamine is a water soluble vitamin that plays a central role in carbohydrate metabolism. It is a key co-enzyme in the multi-enzyme complexes like pyruvate dehydrogenase and alphaketoglutarate dehydrogenase that take part in oxidative decarboxylation of carbohydrates. Thiamine deficiency was described in diabetic patients as early as 1987(9) showed decreased thiamine levels in diabetic outpatients who were not on thiamine supplements. They also hypothesized that marginal thiamine deficiency in diabetic

patients could be due to restricted intake of food-stuffs, reduced absorption, reduced storage capacity, mal-utilizations, increased metabolism or increased excretion of thiamine. One study showed a 75% decrease in plasma thiamine levels in patients with type II diabetes mellitus due to increased renal clearance and fractional excretion of thiamine(10). An animal study done by Rana Chakrabarti et al , showed improvement in the structural damage caused by oxidative stress in diabetic rats leading to tissue necrosis, by using a synthetic lipid soluble derivative of thiamine called benfotiamine(11). He showed that benfotiamine prevented further renal alteration caused by uncontrolled diabetes mellitus. Gadau et al showed an accelerated healing of ischemic diabetic limbs in streptozocin induced diabetic mice, on treatment with benfotiamine, by preventing ischemia induced toe-necrosis and improvement in hind limb perfusion and oxygenation, and restoration of endothelium-dependent vasodilatation(12).

Erythrocyte Transketolase activity and Thiamine Pyrophosphate Effect are methods of determining thiamine deficiency. At present there are no prospective studies that have been carried out in India comparing the thiamine status of the diabetic population.

Hence, thiamine poses as a potential contender for adjunctive therapy in management of diabetic foot complications, both in prevention of diabetic ulcers and for prevention of amputation in the contra-lateral limb after an amputation on one limb. The proposed study is a first prospective study of its kind conducted on diabetic patients in our institution for establishing a correlation between diabetic patients undergoing lower extremity amputations and their thiamine status.

Rationale for the choice of cases and controls

The studies done in the past for measurements of thiamine levels had compared diabetic outpatients with normal age matched volunteers(9,13) and shown a significant decrease in thiamine levels among diabetic patients. With evidence of improved healing of ischemic toe-

necrosis in animal models on treatment with thiamine derivatives(12), the role of thiamine in development of foot ulcers in diabetic patients needed to be explored further. This was the first study in our country which compared thiamine levels in patients undergoing a lower extremity amputation (cases), with non-amputated diabetics (controls).

AIMS AND OBJECTIVES

Aims and Objectives

- **Aims**

  To assess the thiamine status of patients undergoing lower limb amputations due to uncontrolled diabetes mellitus type II.

- **Objectives**

  1. To measure and compare the Erythrocyte Transketolase activity (ETKA) (functional marker of thiamine status) in type II diabetics undergoing lower extremity amputations with non-amputated type II diabetics.
  2. To analyse possible correlation of thiamine deficiency with markers of progression of diabetes mellitus.

- **Null Hypothesis**

  The diabetic patients undergoing lower extremity amputations have no reduction in Erythrocyte Transketolase Activity (ETKA) as compared to diabetic patients without lower extremity amputations.

REVIEW OF LITERATURE

1. Diabetes Mellitus

1.2 Introduction

Diabetes Mellitus denotes a group of common metabolic diseases that share the phenotype of hyperglycaemia. Several types of diabetes are caused by a complex interaction of genes and environmental factors. On the basis of the aetiology of the diabetes, factors contributing to hyperglycaemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dys-regulation associated with diabetes causes secondary pathophysiologic changes in multiple organ systems that impose a heavy burden on the individual with diabetes and on the health care system. In India, diabetes is the leading cause of non-traumatic lower extremity amputations. It also predisposes to cardiovascular diseases. With a booming incidence worldwide, diabetes will be a leading cause of morbidity, and mortality in the foreseeable future.

1.2 Classification

Diabetes is classified according to the pathogenic process that causes hyper-glycaemia. The two broad types of diabetes are as follows:

1. Type 1 or Insulin Dependent Diabetes Mellitus(IDDM)
2. Type 2 or Non-Insulin Dependent Diabetes Mellitus(NIDDM)
3. Others

Type 1 diabetes is the result of complete or near total absence of insulin. Type 2 diabetes is a mixed group of disorders, characterised by different degrees of insulin resistance, impaired insulin secretion and increased glucose production. The third category consists of diabetes due to genetic defects of β cell function (for example MODY 1 to 6), genetic defects in the action of insulin, diseases of the exocrine pancreas, endocrinopathies (example acromegaly,

glucagonoma, Cushing's syndrome), drugs (example glucocorticoids, pentamidine, thiazides) and infections (example congenital rubella, coxsackievirus or cytomegalovirus).

1.3 Diagnosis

The diabetic status of a person can be classified in to three different categories which are

1. Normal glucose homeostasis – when the fasting glucose level is less than 100mg/dl, the post-prandial glucose level is less than 140mg/dl (following an oral glucose challenge) and HbA1C is less than 5.6%.
2. Impaired glucose homeostasis – when the fasting glucose level is between 100 and 125mg/dl, the post-prandial glucose level is between 140 and 199mg/dl (following an oral glucose challenge) and HbA1C is between than 5.7% and 6.4%.
3. Diabetes Mellitus – when the fasting glucose level is more than 126mg/dl, the post-prandial glucose level is more than 200mg/dl (following an oral glucose challenge) and HbA1C is less than 6.5%.

The International Expert Committee with members appointed by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF) has issued diagnostic criteria for DM which is as follows:

1. Symptoms of diabetes plus random blood glucose concentration 200 mg/dl *or*
2. Fasting plasma glucose 126 mg/dl *or*
3. HbA1C > 6.5% *or*
4. Two-hour plasma glucose 200 mg/dl during an oral glucose tolerance test.

1.4 Risk factors and Screening

The ADA recommends screening all individuals more than 45 years of age, every 3 years and screening individuals at an earlier age if they are overweight [body mass index (BMI) >25 kg/m^2] and have one additional risk factor for diabetes. The risk factors for diabetes are as follows:

1. Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
2. Obesity (Body Mass Index of more than 25 kg/m^2)
3. Physical inactivity
4. Previously identified with Impaired Fasting Glucose, Impaired Glucose Tolerance, or an A1C of 5.7–6.4%
5. History of gestational diabetes mellitus(GDM) or delivery of baby >4 kg (9 lb)
6. HDL cholesterol level <35 mg/dl and/or a triglyceride level >250 mg/dl.
7. Polycystic ovary syndrome or acanthosis nigricans
8. Hypertension (blood pressure 140/90 mmHg)
9. History of cardiovascular disease

1.5 Epidemiology

Diabetes is rapidly gaining the status of a potential epidemic in our country. As of 2007, there were more than 62 million individuals in our country that were diagnosed to have diabetes(1,14). According to worldwide estimates made by Wild et al, the prevalence of diabetes mellitus is going to double from 171 million in 2000 to 366 million in 2030 with India having the maximum increase(14). In India, the aetiology of diabetes mellitus is multi-factorial. It includes genetic factors coupled with environmental influences like(2):

1. Obesity
2. Rising living standards
3. Steady Urban migration

4. Lifestyle changes.

With respect to geographical distribution, estimates reveal that the prevalence of diabetes mellitus in rural population is only one-quarter of that of urban population countries in the Indian subcontinent including Bangladesh, Nepal, Bhutan, and Sri Lanka(3,14). A study conducted by the Indian Council of Medical Research suggests that Maharashtra(9.2million) and Tamil Nadu(4.8 million) are more affected than states of Northern India like Jharkhand (0.96 million) or Chandigarh (0.12 million)(3). More studies are needed in our country to highlight the cultural and ethnic trends and give a comprehensive understanding of the differences in diabetes aetiology between Indian and other ethnic groups within India.

There is gross disparity in our country with respect to access to reliable screening methods, anti-diabetic medications and health benefits in urban population as compared to the rural population. Multiple factors like illiteracy, poverty, poor sanitation, food insecurity and dominance of communicable diseases add to the reasons for undermining and under-prioritising the looming threat of diabetes(4), by policy makers and local governments in rural areas

Obesity is a major independent risk factor in diabetes which has found sub-optimal research focus in our country(15). In spite of having lower obesity and overweight rates, India has a higher prevalence of diabetes compared to western data which suggests that diabetes mellitus may occur at a much lower body mass index (BMI) in Indians compared with Europeans(15,16). As a result, relatively lean Indian adults with lesser body mass index may be at equal risk as those who are obese. Additionally, Indians are genetically susceptible to the development of coronary artery disease (CAD) due to dyslipidaemia and low levels of high density lipoproteins (HDL)(17). Hence these determinants make Indians more prone to development of the complications of diabetes at an early age (20-40 years) compared with Caucasians (>50 years) and indicate that diabetes mellitus must be carefully screened and

monitored regardless of patient age within India(17). Inadequate glycaemic control, a factor that has been witnessed in the Indian diabetic population (18) is to blame for the micro- and macro-vascular changes that manifest with diabetes, and can predispose diabetic patients to other complications for instance diabetic myonecrosis(7) and muscle infarction(8).

2. Biochemistry of Insulin

2.1 Biosynthesis

Insulin is produced by the beta cells of the pancreatic islets. Initially, the molecule is a single chain 86 amino acid long precursor polypeptide which is called as pre-proinsulin. Afterwards, proteolysis removes the amino-terminal signal peptide which gives rise to proinsulin.

Further, removal of 31-residue fragment results in the formation of C peptide and the A and B chains of insulin.

2.2 Secretion

The following metabolites regulate the secretion of insulin:

1. Glucose
2. Amino acids
3. Ketones
4. Various nutrients
5. Gastro-intestinal peptides
6. Neurotransmitters

Among the above metabolites, insulin is the most important regulator. Glucose more than 70mg/dl stimulates insulin synthesis by increasing protein translation and processing.

2.3 Action

About 50% of the insulin that enters the portal veins gets degraded by the liver. The rest of the insulin enters the systemic circulation from where it reaches the receptors on the target

sites. Once bound to its receptor, the insulin molecule stimulates tyrosine kinase activity, leading to receptor auto-phosphorylation, and the recruitment of intracellular signalling molecules, such as insulin receptor substrates. This action sets up a phosphorylation and de-phosphorylation cascade which results in the metabolic and mitogenic effects of insulin.

Insulin is an anabolic hormone which increases the storage of carbohydrates and fats and protein synthesis. Brain is the only tissue which consumes glucose in an insulin-independent manner.

3. Complications of Diabetes Mellitus

The complications of diabetes mellitus can be classified as:

1. Acute
2. Chronic

3.1 Acute Complications

The acute complications of diabetes mellitus are more common in individuals with type I Diabetes mellitus. The complications are as follows:

- Diabetic keto-acidosis: It is a condition with the patient presenting with symptoms of nausea/vomiting, thirst and abdominal pain. On examination, the patient would have tachycardia, dehydration or hypotension, tachypnoea or Kussmaul breathing and lethargy. The precipitating events are usually inadequate insulin administration, infection or infarction (cerebral, coronary, mesenteric or peripheral).
- Hyperglycaemic hyperosmolar state: It is a condition with the patient presenting with symptoms of polyuria, loss of weight and diminished oral intake. On examination, the patient has altered mental status and dehydration.

3.2 Chronic Complications

The chronic complications are a major cause of morbidity and mortality in the medical and surgical wards. The complications can be divided in to two broad types which are vascular and non-vascular. The vascular complications are as follows:

3.2.1 Micro-vascular Complications:

1. Neuropathy
    a. Sensory neuropathy
    b. Motor Neuropathy (mono or polyneuropathy)
    c. Autonomic Neuropathy
2. Nephropathy
3. Ophthalmopathy
    a. Retinopathy (proliferative / non-proliferative)
    b. Macular oedema

3.2.2 Macro-vascular complications:

1. Coronary Heart Disease
2. Peripheral Arterial Disease
3. Cerebrovascular Disease

3.2.3 Other Complications

1. Gastro-intestinal
    a. Gastro-paresis
    b. Diarrhea
2. Genito-Urinary
    a. Diabetic Uropathy
    b. Sexual Dysfunction

c. Susceptibility to Infections

d. Cataract

e. Glaucoma

f. Peri-odontal Disease

g. Hearing loss

3.3 Mechanisms of Complications

Chronic hyperglycaemia is one of the most important factors for development of complications of Diabetes Mellitus. However the actual mechanism that leads to the diverse cellular and organ dysfunction is unknown. There were four theories that have been proposed to explain as to how hyperglycaemia leads to the chronic complications of Diabetes Mellitus.

1. The first theory suggests that elevated intracellular glucose leads to the formation of Advanced Glycosylation End products (AGEs). These AGEs cause non-enzymatic glycosylation reactions of the proteins present in the intra-cellular space and extra-cellular space and have been shown to have the following effects :
    a. Cross-linking of proteins like collagen and extracellular matrix proteins
    b. Accelerate atherosclerosis
    c. Promote glomerular dysfunction
    d. Reduce nitric oxide synthesis
    e. Induce endothelial dysfunction
    f. Alter extracellular matrix composition and structure
2. The second theory advocates the observation that hyperglycaemia increases glucose metabolism via the sorbitol pathway. The elevated concentration of sorbitol has the following effects:
    a. Changes the redox potential of the cell
    b. Increases cellular osmolality

c. Generates reactive oxygen species

3. The third theory supports the idea that chronic hyperglycaemia leads to excess formation of diacylglycerol which leads to the activation of Protein Kinase C or PKC. PKC alters the transcription of genes for, type IV collagen, fibronectin, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons. PKC inhibitors are being studied in trials for treatment of diabetic nephropathy.
4. The fourth theory recommends that chronic hyperglycaemia increases the flux through hexosamine pathway. This pathway generates fructose-6-phosphate which is substrate for O-linked glycosylation and proteoglycan production. The proposed increase in function of the hexosamine pathway alters the glycosylation of proteins like endothelial nitric oxide synthase.

Overall, growth factors seem to play an essential role in some Diabetes related complications, and their production is augmented by most of these proposed pathways. For example, the Vascular endothelial growth factor (VEGF-A) is found to be elevated locally in proliferative diabetic retinopathy and decline after laser photocoagulation.

4. Prevention of Complications of Diabetes

The complications of diabetes mellitus are a source of grave concern for the health care professionals. Hence, the factors helping in prevention of these complications are a matter of constant research. The Diabetes Control and Complications Trial (DCCT) gave conclusive proof in 2014 that reduction in the chronic hyperglycaemia will prevent the early complications of Diabetes Mellitus type I, by randomizing 1400 individuals with Type I Diabetes Mellitus to either conventional or intensive diabetes management(19). The DCCT established that improvement of glycaemic control reduced non-proliferative and proliferative retinopathy (47% reduction), micro-albuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction).

Another trial called ‘United Kingdom Prospective Diabetes Study (UKPDS)’ studied the course of more than 5000 individuals with Diabetes Mellitus type 2 for more than 10 years(20). In this study, newly diagnosed patients with Diabetes Mellitus Type II were randomized to two groups, one being intensive treatment with insulin and one of the oral hypoglycaemic agent(either a sulfonylurea or metformin) and the other being conventional treatment using diet modification and pharmacotherapy. The UKPDS established that each percentage point reduction in A1C was associated with a 35% decrease in micro-vascular complications.

Another landmark finding of the UKPDS was that strict control of blood pressure considerably reduced both macro-vascular and micro-vascular complications(20). In fact, the advantageous effects of blood pressure control were more than the beneficial effects of glycaemic control. Lowering blood pressure to moderate goals (144/82 mmHg) decreased the risk of Diabetes-related mortality, stroke, micro-vascular end- points, retinopathy, and heart failure (risk reductions between 32 and 56%).

4.1 Diabetic Neuropathy

The diabetic neuropathies are mixed group, involving various parts of the nervous system that present with varied clinical manifestations. These neuropathies may be either focal or diffuse. The most frequently occurring, among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN) and the autonomic neuropathies(21).

The early acknowledgement and suitable management of neuropathy in the individual with diabetes is imperative because:

1. Up to 50% of distal symmetric polyneuropathy may be asymptomatic, and individuals suffering from the same are at a risk of insensate injury to their feet. As

more than 80% of amputations follow a foot ulcer or injury, early diagnosis of 'at-risk' individuals, providing education, and appropriate foot care may result in a decreased incidence of ulceration and therefore amputation.

2. Autonomic neuropathy causes considerable morbidity and mortality, especially if cardiovascular autonomic neuropathy (CAN) is present.

Definition of Diabetic Peripheral Neuropathy

At present the definition of DPN in clinical practice is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes"(22). This definition clarifies that not all patients suffering from peripheral nerve dysfunction have a neuropathy due to diabetes. Validation of the same can be verified with quantitative electrophysiology, sensory, and autonomic function testing.

4.1.1 Types of Diabetic neuropathy

1. Acute Sensory Neuropathy
2. Chronic Sensory-motor Neuropathy

Acute sensory neuropathy

Acute sensory neuropathy is very uncommon and has a tendency to follow episodes of poor metabolic control (e.g., ketoacidosis) or sudden worsening in glycaemic control (aka, "insulin neuritis"), and is characterized by the acute onset of severe sensory symptoms with marked nocturnal exacerbation but few neurologic signs on examination of the legs.

Chronic sensorimotor neuropathy

This is the most frequently seen presentation of neuropathy in diabetes, and up to 50% of diabetics may have symptoms, most commonly burning pain, stabbing or electrical sensations, paraesthesias, hyperesthesia, and deep aching pain. Neuropathic pain is

characteristically worse at night, and the symptoms are mostly experienced in the feet and lower limbs though in some cases the hands also may be affected. Since up to half the patients may not have symptoms, a diagnosis may only be made on examination or, as seen in in some cases, the patient come with a painless foot ulcer.

Examination of the lower limb typically has sensory loss of vibration, pain, pressure and temperature perception (mediated by small and large fibres) and absent ankle reflexes. Frequently signs of peripheral autonomic (sympathetic) dysfunction are often seen and include a warm or cold foot, occasionally with distended veins on dorsum of foot (in the absence of obstructive peripheral vascular disease), dry skin, and the presence of calluses on pressure-bearing area

The diagnosis of DPN can be made only after a thorough clinical examination, and all diabetic patients should be screened annually for DPN by examining temperature, pinprick, and vibration perception (using a 128-Hz tuning fork, see figure 1), 10-g monofilament pressure sensation at the distal halluces, and ankle jerk reflexes. Combinations of more than one test have >87% sensitivity in identifying DPN(21). Absence of 10-g monofilament perception and decreased vibration perception foretell foot ulcers. Also, longitudinal studies have revealed that a simple clinical examination is a good predictor of foot ulcer risk in the future(23). The feet should be regularly examined for calluses, ulcers and deformities, and the footwear should be inspected. Multiple scoring systems have been devised for monitoring the progression or response to intervention in clinical trials.

Figure 1

Figure 2

Figure 3

Other forms of neuropathy, including B12 deficiency, chronic inflammatory demyelinating polyneuropathy (CIDP, hypothyroidism, and uraemia, occur more commonly in diabetes and should be excluded.

4.2 Diabetic Foot Ulcers

Diabetic foot pathologies like infections, ulcerations and gangrene, are the most common cause of hospitalization amongst the diabetic patients(24). McNeely and his colleagues postulated that the majority of foot ulcers resulted from minor trauma in the presence of sensory neuropathy(25). Even though the pathogenesis of diabetic peripheral sensory neuropathy is still not fully understood, there appears to be several mechanisms involved, including the generation of advanced glycosylated end products (AGEs) and diacyl-glycerol, oxidative stress as well as activation of protein kinase C β. Additionally, the Diabetes Control and Complications Trial(19) and other prospective trials have established the crucial role of hyperglycaemia in the onset and progression of neuropathy. The data connecting glycaemic control and neuropathy were not as well defined as those for retinopathy due to the difficulty in categorizing objective measures to gauge the many stages of neuropathy over time and also since the symptoms, or lack thereof, of neuropathy may be misleading if assessed only through patient questionnaires.

4.3 Scoring systems in Diabetic Neuropathy

Dyck and colleagues pioneered the use of composite scores to evaluate clinical signs of diabetic neuropathy(26,27). Their team described the diabetic neuropathy symptom score, neuropathy disability score (NDS) and later the Neuropathy Impairment Score (NIS). Several

large studies have used the modified NDS as shown in figure 4(23,28,29) and also, it can be used in the community by a trained non-specialist.

NDS

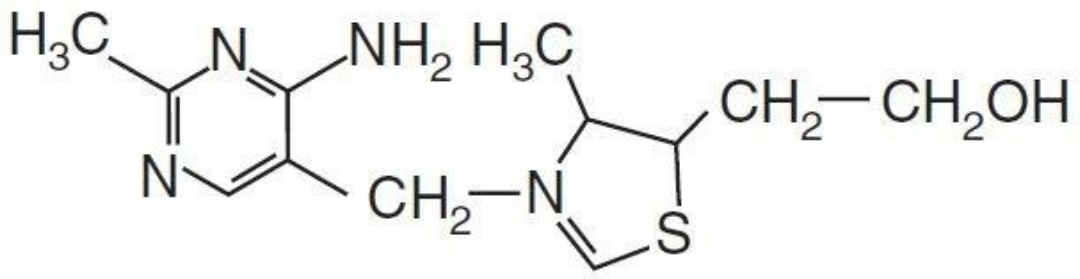
		Right	Left
VPT 128 Hz tuning fork; apex of big toe: normal = can distinguish vibrating/not vibrating	Normal = 0; abnormal = 1		
Temperature perception on dorsum of the foot Use tuning fork with beaker of ice/warm water			
Pin prick Apply pin proximal to big toenail just enough to deform the skin; trial pair = sharp, blunt; normal = can distinguish sharp/not sharp			
Achilles reflex	Present = 0 Present with reinforcement = 1 Absent = 2		
	NDS total out of 10		

Figure 4 Modified Neuropathy disability Score VPT – Vibration Perception Threshold.

Diabetic neuropathy symptom score (DNS)

DNS items	Rate
Unsteadiness in walking	0 = absent, 1 = present
Numbness	0 = absent, 1 = present
Burning, aching pain or tenderness in legs or feet	0 = absent, 1 = present
Prickling sensations	0 = absent, 1 = present

5. Thiamine

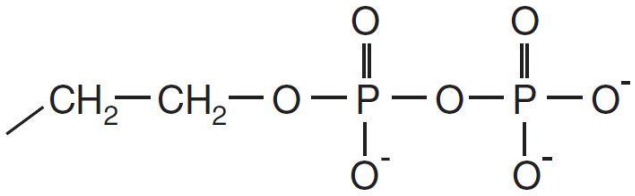


THIAMINE MOLECULE

Thiamine or Vitamin B 1 has a quintessential role to play in the energy-generating metabolism and especially the metabolism of carbohydrate. It can exist in our body as thiamine monophosphate and thiamine diphosphate. Thiamine diphosphate(figure 6) is one of the co-enzymes in the three multi-enzyme complexes that catalyse oxidative decarboxylation reactions which are the following:

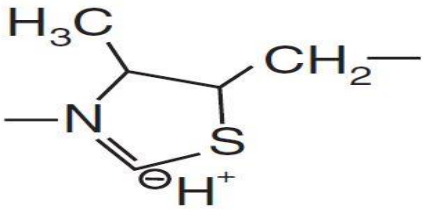
1. Pyruvate dehydrogenase in carbohydrate metabolism
2. Alpha – ketoglutarate dehydrogenase in citric acid cycle
3. Branched chain keto-acid dehydrogenase involving the metabolism of valine, leucine or isoleucine.

It is also useful as a co-enzyme in the pentose pathway for transketolase. In each of these complex pathways, the role of thiamine diphosphate is to provide a reactive carbon on the thiazole moiety that leads to formation of a carbanion(figure 7). This carbanion adds to the carbonyl group of pyruvate, alpha-ketoglutarate or the branched chain keto-acid as required in the respective complexes



Thiamin diphosphate

Figure 5



Carbanion

Figure 6

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The discovery of thiamine dates back to the late 1890's, when the Dutch medical officers Eijkman and Grijns, who were working in Java, showed that a paralytic illness resembling beriberi could be produced in chickens by feeding them a diet solely consisting of polished rice(30). Human experiments were conducted in a mental asylum and in a railroad labour camp in the Malay States, where half of the subjects were fed polished rice, and the other half were given brown rice, from which the polishings hadn't been removed(31). Beriberi always manifested in the white rice groups.

Jansen and Donath in 1926 isolated the anti-beriberi factor, vitamin B_1, as crystals from a water extract of rice bran. In 1936, Williams identified and published the chemical formula and named it thiamine, referring to the amino and thiazole groups in the molecule. One year later, improvement in the methods of synthesis led to the first commercial manufacture of the vitamin.

5.1 Chemistry of Thiamine

The thiamine molecule is white crystalline, water soluble solid. In the crystallized state or in an acidic medium the stability of thiamine is good, even on heating. In a neutral or alkaline medium, thiamine is unstable and sensitive to oxygen, heat and ultraviolet light.

Thiamine is a water-soluble vitamin and its absorption takes place in the jejunum. The absorption occurs via an active transport portal (when the thiamine levels in the small intestines are low) or via a passive mucosal process (when thiamine concentration is high). Phosphorylation of thiamine takes place in the small intestine(32) and gets converted to active co-enzyme thiamine pyrophosphate. The body itself cannot synthesize thiamine but can only store up to 30 mg of it in the tissues and is mostly concentrated in our skeletal muscles. The other organs, in which it is stored, are the brain, liver, heart and kidneys. Although all cell types use thiamine, the nervous system is especially sensitive to thiamine deficiency due to its role in the production of acetylcholine and γ-aminobutyric acid in our brain. Also the heart is extremely sensitive to thiamine deficiency due to the high level of oxidative metabolism. The half-life of thiamine is 9-18 days. Thiamine is excreted by kidneys and its rate is determined by its tubular reabsorption, glomerular filtration and also on plasma thiamine concentration(33).

5.2 Intra-Cellular Thiamine Metabolism

Thiamine and Thiamine Monophosphate are the most abundant forms found in the plasma. Uptake of thiamine and its monophosphate (TMP), by cells is mediated by particular thiamine transporters 1 (THTR1 encoded by SLC19A2 gene) and 2 (THTR2 encoded by SLC19A3) and RFC1 (Reduced Folate Carrier – 1). Most of thiamine in the cytoplasm (around 90%) is phosphorylated by TPK1 (Thiamine Phosphokinase) to TDP (Thiamine di phosphate) and used as a cofactor of cytoplasmic enzymes while the remaining thiamine stays un-phosphorylated(34). Most of the Thiamine Di-phosphate (approximately 90%) is transported into mitochondria through the thiamine transporter from the solute carrier group of proteins encoded by the SLC25A19 gene. The intracellular mechanism of thiamine is summarized in the figure 8 below (35)

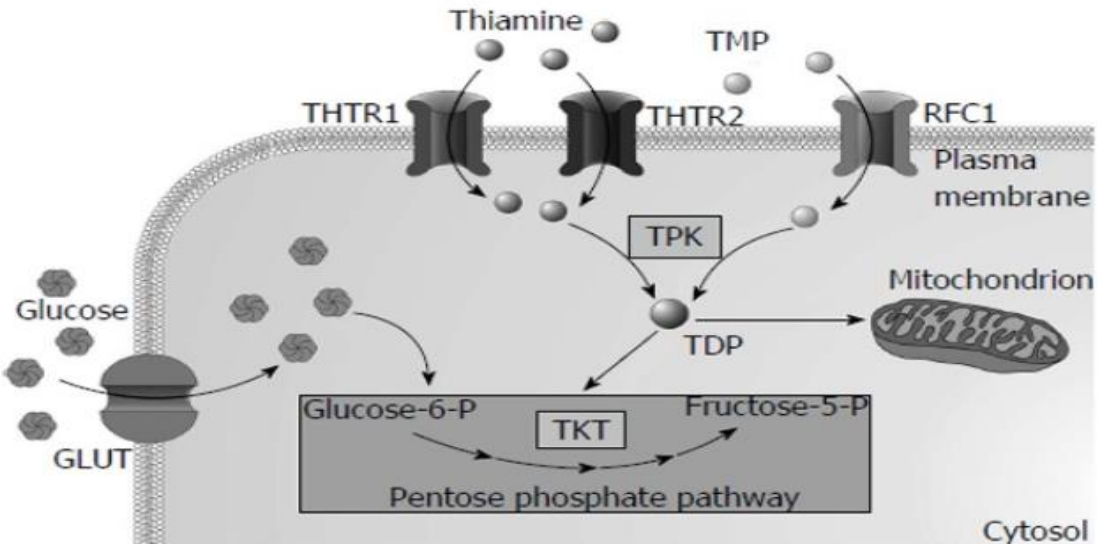


Figure 7

Since the body is unable to store thiamine and the vitamin has a great turnover rate, a constant supply of the vitamin is needed. The limited stores may be exhausted within two weeks or less on a thiamine-free diet, with clinical signs appearing shortly thereafter. The body is readily depleted of thiamine by fever and other metabolic stress. The heart, liver, kidney and brain have the highest levels, followed by the leukocytes and the red blood cells (F. Hoffman-LaRoche, 1994). De-phosphorylation can occur in the kidney and excess free vitamin is rapidly excreted in the urine. The urinary elimination depends partly on the urine volume and during diuresis large amounts of thiamine may be lost. Small quantities of thiamine are excreted in sweat.

The foodstuffs rich in thiamine are the following(32):

1. Whole-grain foods
2. Meat/fish/poultry/eggs
3. Tomato and orange juices
4. Milk and milk products
5. Legumes (like lentils, soybeans, nuts, seeds)

6. Vegetables (like green, leafy vegetables; beets; potatoes)

The foodstuffs containing thiaminases, like milled rice, shrimp, fresh fish, mussels, clams and raw animal tissues, reduce the absorption of thiamine.

5.3 Thiamine deficiency

It is a clinical syndrome that arises as a result of either of the following factors:

1. Lack of thiamine intake in the diet:
    a. Food having a elevated level of thiaminases, including milled rice, raw freshwater fish, ferns and raw shellfish.
    b. Consumption of foodstuffs high in anti-thiamine factor, like tea, coffee, or betel nuts.
    c. Processed food with high amounts of sulphite in it, which destroys thiamine.
2. Diet-related factors causing reduced thiamine intake:
    a. Starvation state
    b. Alcoholic state
    c. Gastric bypass surgery - Due to limited caloric intake during postsurgical repair(36–38).
    d. Parental nutrition with insufficient thiamine supplementation(39).
3. Increased consumption states:
    a. Hyperthyroidism(40)
    b. Pregnancy
    c. Diets high in carbohydrate or saturated fat intake
    d. Lactation
    e. Fever - Severe infection/sepsis (41)
    f. Increased physical exercise

g. Re-feeding syndrome (carbohydrate metabolism is increased)

4. Increased Depletion(13):
    a. Diarrhoea
    b. Diuretic therapies
    c. Peritoneal dialysis
    d. Haemodialysis/continuous renal replacement therapy
    e. Hyperemesis gravidarum

It is expressed in the initial stages by anorexia, malaise, and weakness of the legs, often with paraesthesia; there may be slight oedema and palpitations. The disorder may continue in this chronic state or may at any time escalate to an acute condition characterized either by cardiac involvement with oedema or by peripheral neuropathy; forms intermediate between these two extremes may also exist. It is thought that the basic cause is the inhibition of a series of enzyme-catalysed cleavages of carbon-carbon bonds in which thiamine di-phosphate is a coenzyme.

The deficiency is known as beriberi, Ceylon sickness, oriental beriberi or rice disease. The outbreaks of beriberi are commonly seen in displaced and refugee populations. Thiamine deficiency occurs mainly where the diet consists of milled white cereals, as well as polished rice, and wheat flour which are all very poor sources of thiamine. Thiamine deficiency can occur within 2-3 months of a poor intake and can cause disability and death. Thiamine deficiency in refugees has been reported in Thailand at the start of the 1980's and in the 1990's, Djibouti (1993) in Guinea (1990), and in Nepal (1993-1995).

In Europe, North America and Australia, thiamine deficiency is prevalent among alcoholics and typically manifests itself as the Wernicke-Korsakoff syndrome but has also been described in patients on controlled diets for obesity, those who received total parenteral

nutrition and in those who are on fad diets or whose intakes are high in carbohydrate and low in thiamine.

5.4 Risk factors for thiamine Deficiency

The great epidemics of thiamine deficiency in South-East Asia at the start of this century followed the large scale production of milled rice and its distribution. The availability of milled rice as an inexpensive and popular food in urban areas was also a reason for the occurrence of thiamine deficiency in these areas. The requirement of thiamine is amplified when carbohydrates are taken in large volumes and is higher during periods of increased metabolism which are:

1. Fever
2. Muscular activity
3. Hyperthyroidism and
4. During pregnancy and lactation

A diet based on polished rice is rich in carbohydrates which enhances the thiamine requirement and is worsened by low thiamine content. Rolfe and his colleagues deduced in 1993 that the risk factors for thiamine deficiency were(42)

1. Pregnancy
2. Alcohol consumption
3. Chronic disability
4. Exercise
5. Diabetes and
6. Dysentery

5.5 Signs and Symptoms of Thiamine Deficiency

Thiamine deficiency in adults can manifest as one of the following two syndromes which are:

1. Thiamine deficiency with peripheral neuropathy
2. Thiamine deficiency with cardiopathy

5.5.1 Thiamine deficiency with Peripheral Neuropathy

It is an acute type of thiamine deficiency categorized by polyneuropathy with paraesthesia of the extremities (mainly the legs), decreased knee jerk and other tendon reflexes, and progressive profound weakness and wasting of muscles and the vulnerability to infections is also increased. This syndrome is also known as dry beriberi, atrophic beriberi, endemic polyneuritis, pan-neuritis endemica, paralytic beriberi or polyneuritis endemica.

Another distinct presentation of neurological involvement is Wernicke encephalopathy, in which an orderly sequence of symptoms, occurs which include vomiting, horizontal nystagmus, palsies of the ocular movements, fever, ataxia, and worsening mental impairment leading to Korsakoff syndrome(43–45). Treatment can be initiated at any stage by the addition of thiamine, unless the patient is in fulminant Korsakoff syndrome. Only half of the patients treated at this stage improve significantly.

5.5.2 Thiamine deficiency with cardio-pathy

An acute form of thiamine deficiency categorised by oedema (mainly of the legs, but also involving the trunk and the face), increased cardiac output, ventricular dysfunction, sinus rhythm, dilatation of arterioles, depressed erythrocyte and leukocyte transketolase, elevated serum lactates and pyruvates, and pulmonary congestion with pleural effusion. In this condition, death from congestive cardiac failure may occur abruptly.

A less common fulminant variant is summarized by lactic acidosis, hypotension, tachycardia, and pulmonary oedema (which eventually cause the death); this is labelled thiamine

deficiency with lactic acidosis. The other names for this condition are wet beriberi, beriberi heart disease, cardiovascular or Shoshin beriberi.

The deficiency of thiamine is occasionally confounded by presence of symptoms of multiple deficiencies like Vitamin B, Vitamin C and other minerals. Many cases of thiamine deficiency show a combination of the above two described syndromes.

5.6 Clinical Diagnostic Criteria for Thiamine Deficiency

MSF/Epicentre (1992) defined a suspect case of thiamine deficiency as a person having at least two of the following signs:

• Bilateral oedema of the lower limbs,

• Dyspnoea with exertion or at rest,

• Paraesthesias of the hands or feet or a symmetrical decrease in muscle strength or motor deficits: stepping or loss of balance.

5.7 Biochemical detection of thiamine deficiency

The diagnosis of beriberi can be done by a dietary history suggestive of a low thiamine intake and clinical signs. However, independent biochemical tests of thiamine status, particularly measurement of erythrocyte transketolase activity (ETKA) and thiamine pyrophosphate effect (TPPE), offer a sensitive test for thiamine deficiency where the laboratory facilities are available(46).

Detection of free thiamine in the blood plasma does not necessarily reflect a direct relationship to the level in the body tissues. Erythrocyte or leucocyte thiamine values actually show a more accurate relationship to tissue content (47). Hence, erythrocyte transketolase activity, the activity of the thiamine-requiring enzyme transketolase, seems to provide information as to tissue reserves of thiamine and mirrors a direct functional assessment at the cellular level. The assay for transketolase or TPPE is performed in the presence and absence

of added thiamine and expressed as an activity coefficient. The values without additional thiamine reveal the amount of coenzyme present in the cells.

The stimulation with further thiamine pyrophosphate gives the measure of apo-enzyme present that lacks coenzyme. Hence, the thiamine pyrophosphate effect or TPPE is expressed as the percentage rise in ETKA obtained after addition of Thiamine Pyrophosphate to the erythrocyte. The biochemical diagnostic criteria of thiamine deficiency is defined by low ETKA and high TPPE (Table 1)(48).

Table 1

Classification of thiamine pyrophosphate effect (TPPE) in individuals

Thiamine condition	TPPE
Normal	0–14 %
Marginally deficient	15–24 %
Severely deficient (with clinical signs)	25+ %

Source: Brin et al(1965)

Urinary thiamine levels can also offer information regarding the sufficiency of dietary intakes, but they don't provide information regarding the state of deficiency, or the extent of depletion of the tissue thiamine reserves. At recommended consumptions, urinary excretion of thiamine ranges from 40 to 90 micrograms per day. When intake is poor, urinary excretion falls below 25 micrograms per day. A link between the urinary excretion of thiamine per gram of Creatinine and thiamine intake has been observed. Table 2 summarizes the interpretive guidelines for the urinary excretion of thiamine(49). Analyses of 24-hour urine collections provided more consistent information than random sample collections. In clinically apparent cases of thiamine deficiency, the 24-hour urinary excretion of 0 to 15 micrograms of thiamine had been reported(49). Further information as to the physiological state with respect to thiamine could be obtained from the test-dose procedure. The most commonly used procedure is to give 5 mg of thiamine parenterally and then measure the

urinary excretion of thiamine over the next 4-hour period (see Table). Although the test may not precisely identify clinical thiamine deficiency or point toward the severity of the deficiency, it can be used as an indicator of poor intakes and tissue deficits of the vitamin (49).

Table 2

Guidelines for the interpretation of urinary excretion of thiamine

Subjects	Deficient (high risk)	Low (medium risk)	Acceptable (low risk)
Urinary thiamine, • g/g creatinine			
1 to 3 years	< 120	120–175	176
4 to 6 years	< 85	85–120	121
7 to 9 years	<70	70–180	181
10 to 12 years	<60	60–180	181
13 to 15 years	< 50	50–150	151
adults	< 27	27–65	66
pregnancy			
2nd trimester	<23	23–54	55
3rd trimester	<21	21–49	50
Urinary thiamine , • g per 6 or 24 hours			
adults: per 24 hr	< 40	40–99	100
per 6 hr	< 10	10-24	25
Load test (return of 5 mg thiamine dose)			
adults: % return of thiamine load in 4hr	< 20	20–79	80

Source: Adapted from Sauberlich HE, Skala JH, Dowdy RP. Laboratory tests for the assessment of nutritional status. Cleveland, Ohio, CRC Press, 1974.

Therefore, to summarize, the following methods of detection of thiamine deficiency can be carried out:

1. Blood thiamine: Blood has only about 0.8% of the total body store of thiamine, and the concentration is too low to permit exact extrapolation of the total thiamine status.
2. Urinary thiamine excretion: The estimation of urinary thiamine excretion is poorly reliable method for judging tissue stores, and similar to the blood levels, is really only a reflection of the immediately preceding intake. Clinical signs of deficiency have

been noted when less than 70micrograms of a 1 mg dose of thiamine is excreted in the urine in a dose-retention test(50).

3. Pyruvate and lactate: Thiamine is necessary for pyruvate metabolism. Therefore, increased blood pyruvate and lactate levels can be triggered by thiamine deficiency. In thiamine deficiency, the fasting levels of blood pyruvate have often been found to be normal and only increase above the normal following a glucose load (51). The estimation of blood pyruvate could be of help in the diagnosis of suspected thiamine deficiency. But it is not appropriate for the detection of minimal thiamine deficiencies in view of restrictions in the sensitivity of this index. An elevated pyruvate level isn't always attributable to thiamine deficiency.
4. Transketolase activity / thiamine pyrophosphate effect: One of the most dependable indicators of thiamine functional status is the activity of the thiamine-requiring enzyme trans-ketolase. The level of trans-ketolase activity allows for judgement on the availability of thiamine.

6. THIAMINE AND DIABETIC COMPLICATIONS

Hyperglycaemia (the aggregate exposure to elevated glucose levels, as well as individual pattern of glucose variation) along with increased availability of free fatty acids (a consequence of unregulated lipolysis in adipose tissue as well as their “spill over” in case of adipocyte saturation in obese subjects) are the two main metabolic alterations characterising gluco-toxicity and lipo-toxicity in diabetes and are causally responsible for the development of vascular complications.

Enhanced glucose supply fuels its intracellular metabolism (glycolysis) with subsequent increase in the generation of reactive oxygen species (ROS) in mitochondria(52,53) . Overproduction of these reactive oxygen species in mitochondria links hyperglycaemia with activation of several biochemical pathways involved in the development of micro vascular complications of diabetes which include hexosamine and polyol pathways, production of advanced glycation end products (AGEs) and activation of protein kinase C(54). It does so by inhibition of the key glycolytic enzyme glyceraldehyde3phosphate dehydrogenase.

However, cells in our body are adept in either lowering the excess production of ROS by non-enzymatic and enzymatic antioxidant mechanisms and/or removal of damaging metabolites and their substrates (produced by excess glycolysis) that accumulate within cells. Pentose phosphate pathway (PPP) is an example of the second mechanism. PPP gives a substitute pathway for glucose oxidation accomplishing three important functions which are(35):

1. Production of reducing equivalent NADPH required for decreasing oxidized glutathione thereby supporting intracellular antioxidant defence.
2. Production of ribose-5-phosphate necessary for the synthesis of nucleotides.
3. Metabolic use of Pentoses obtained from the diet.

The Pentose Phosphate Pathway has the following two branches:

1. Irreversible oxidative branch required for pentose phosphates and NADPH production.
2. Reversible non-oxidative branch in which inter-conversion of three to seven carbons containing sugars take place.

Transketolase (TKT), one of the vital enzymes of non-oxidative branch of Pentose Phosphate Pathway, can limit the activation of harmful pathways by decreasing the availability of their precursors. Transketolase transports two carbon units and catalyses synthesis of ribose-5-phosphate from intermediates of glycolytic pathway. Thiamine, as a cofactor of Transketolase, may have a great influence on glucose metabolism through the regulation of Pentose Phosphate Pathway and therefore, Transketolase activation by Thiamine in endothelial cells blocked numerous pathways responsible for hyperglycaemic injury and stopped the development and progression of diabetic complications in animal models(55). The fundamental tool responsible for the observed effect of thiamine or its derivative benfotiamine upon activation of non-oxidative reversible branch of Pentose Pathway was the diminished build-up of triose-phosphates and fructose-6-phosphate induced by hyperglycaemia(56).

Plasma thiamine levels are decreased in diabetics by 75% as compared to healthy subjects(10). The Reduced Folate Carrier (RFC1) and THTR1 protein expression in RBCs obtained from diabetic patients (both T1DM and T2DM) is higher than in normal healthy subjects(10).

Experimental proof suggests anomalous thiamine handling in our kidneys in diabetes mellitus which might be one of the causes for reduced plasma thiamine levels in diabetics. Incubation of human primary proximal tubule cells in excess glucose conditions (26 mmol/L) reduces both mRNA and protein expression of THTR1 and THTR2 as compared to 5 mmol/L glucose

(57). The renal clearance of thiamine is amplified 8-fold in experimental models of diabetes. Remarkably, increased clearance was prevented by high dose thiamine supplementation(58).The renal clearance of Thiamine was also increased in subjects with Type I Diabetes Mellitus by 24 fold and Type 2 Diabetes Mellitus by 16fold(10)

Additional changes in thiamine metabolism possibly occur with the development of chronic diabetic micro-vascular complications like diabetic nephropathy along with chronic kidney disease (CKD). Although in diabetics with intact renal function, the plasma thiamine levels tend to be decreased mostly due to elevated renal clearance, in subjects with CKD stages consistent with renal insufficiency and failure the situation dramatically changes. Plasma levels of thiamine and its esters and Erythrocyte TKT activity increased with severity of diabetic nephropathy (and CKD respectively) being maximum in subjects with end stage renal disease, however, levels of Thiamine Di-phosphate in RBCs did not show proportional trend. Since the effectiveness of intracellular Thiamine Di-Phosphate production relies on the substrate availability (i.e., the rate of trans-membrane transport via thiamine transporters) and Thiamine Pyrophosphokinase (TPK) activity, these could be the processes reduced by hyperglycaemia and the contributory reasons for the failure of protective action of Pentose phosphate pathway under hyperglycaemia(35). Although Type 1 and Type 2 Diabetic patients with normal kidney function have been shown to have an increased expression of THTR1 and THTR2 in mononuclear cells as compared to healthy subjects by one study (59), data on TPK activity and THTR2 expression in diabetes are still missing and warrant further study.

6.1 Supplementation of Thiamine in Human, Animal and In Vitro models in Diabetic Conditions

6.1.1 Human Studies

Very few studies have been published on diabetic patients till now, that elaborated the effect of thiamine or benfotiamine (the synthetic form of thiamine) treatment on definitive endpoints like the development or progression of clinically evident diabetic complications, i.e. kidney disease, ophthalmopathy and neuropathy. In the pilot study by Rabbani and his colleagues, high dose thiamine therapy given for 3 months significantly reduced urinary albumin excretion without altering glycaemic control, lipids and blood pressure in T2DM patients(60). Another study done by Alkhlef and his team however, showed that three months of benfotiamine therapy enhanced the thiamine status (assessed by the Transketolase activity and the whole blood thiamine levels) but did not change the urinary albumin excretion and kidney markers of tubular damage in patients with type 2 Diabetes Mellitus(61). The same team also assessed the production Advanced Glycosylation End production (AGEs) and markers of endothelial dysfunction and low grade inflammation in the same cohort of subjects. Benfotiamine did not alter any of the ascertained markers(62). In patients suffering from diabetic neuropathy, short term benfotiamine therapy was found to improve neuropathy score and to lower the pain perception(63). In a study done recently, long term (one year) benfotiamine supplementation therapy did not alter the peripheral nerve function and soluble markers of inflammation (like interleukin6 or E-selectin) in spite of significantly increasing the whole blood levels of thiamine and Thiamine Di-phosphate in patients with Type 1 Diabetes Mellitus(64). This study was criticized for incorrect study design and the definition of its endpoints(64).

6.1.2 Animal Studies

For animals, the first published study investigating the effect of supplementation of thiamine and benfotiamine on peripheral nerve function and generation of AGEs in diabetic rats discovered that benfotiamine but not thiamine had a protective effect on both processes(65). Hammes and his colleagues provided proof for the role of Pentose Phosphate Pathway in diabetes showing that benfotiamine (activating Transketolase) blocked three harmful pathways and NF-κ signalling triggered by hyperglycaemia and prevented progression of diabetic retinopathy in experimental rats(55). Thornalley and his group had published a series of articles exploring the effect of thiamine and/or benfotiamine supplementation on the development of diabetic micro-vascular complications, mainly diabetic kidney disease. They found that thiamine and its synthetic preparation were able to lower the accumulation of AGEs in the nerves, eyes, kidneys and plasma of diabetic rats(66). Moreover, they also reported that high dose benfotiamine and thiamine therapy prevented diabetic nephropathy due to the increased Transketolase expression, lowered level of triose-phosphates and decreased protein kinase C activation. Most notably, since no alterations in fasting plasma glucose and HbA1c were detected, this effect is independent of diabetic control(57).

Moreover, high-dose thiamine therapy had positive effect on diabetes related dyslipidaemia (checking the increase of triglycerides and plasma cholesterol but not high density lipoprotein decrease). Low dose thiamine and Benfotiamine failed to achieve the same effect(67). They also measured AGEs in plasma of rats with induced diabetes. Both benfotiamine and thiamine supplementation have been shown to stabilize AGEs derived from methyl-glyoxal and glyoxal. On the other hand, carboxy-methyl lysine and N-epsilon(1carboxyethyl) lysine residues were decreased by thiamine only(68). Finally, they calculated protein damage caused by oxidation, glycation, oxidation and nitration in diabetic rats and found elevated

content of AGEs in the diabetic nerve, eye, kidney and plasma that was reversed on administration of benfotiamine and thiamine. The increase of plasma glycation free adducts was also reversed by Thiamine. Administration of both thiamine and benfotiamine reversed the elevated urinary excretion of oxidation, glycation and nitration free adducts(69). Multiple studies investigated the effect of treatment with thiamine/benfotiamine with respect to cardiac function in diabetic animal models and found out that Benfotiamine improved abnormalities in parameters related to the contractile dysfunction in diabetic mice. In these studies, although the generation of AGEs did not change, the oxidative stress induced by diabetes was reduced(70). Kohda and his colleagues elaborated that high dose therapy with thiamine averted diabetes related cardiac fibrosis through amplified expression of genes with pro-fibrotic effect and reduced matrix metalloproteinase activity in hearts of diabetic rats(71). Another study done by Katare and his team discovered that therapy with benfotiamine prevented cardiac failure in diabetic mice. There were several pathogenic mechanism suggested like

- Improved cardiac perfusion
- Reduced fibrosis
- Cardio-myocyte apoptosis(72).

The same team also found that benfotiamine enhanced prognosis of diabetic mice after a myocardial infarction with respect to functional recovery, survival, decreased cardio-myocyte apoptosis and neuro-hormonal activation(73). Similar results were also found in the control non-diabetic mice which were perhaps due to elevated activity of pyruvate dehydrogenase in the cardiac myocytes of diabetic rats on treatment with thiamine. Consequent *in vitro* experiment showed that the responsible molecular mechanism may be suppression of O-glycosylated protein(74). Both *in vitro* and *in vivo* supplementation of benfotiamine had positive effect on cardiac progenitor cells in terms of their functionality, proliferation,

abundance and Transketolase activity (all listed parameters being compromised by hyperglycaemia)(75). In mice with induced diabetes with limb ischemia benfotiamine increased the Transketolase activity, prevented toe necrosis, enhanced perfusion and restored vasodilation. Furthermore, benfotiamine prevented build-up of AGEs in blood vessels and inhibited pro-apoptotic caspase-3 in muscles(12). Another study investigated the cerebral oxidative stress in diabetic mice and reported that benfotiamine was found to decrease oxidative stress (as projected by reduced/oxidized glutathione). Although the levels of AGEs, protein carbonyl and tumour necrosis factorα remained unchanged(76). Therapy with benfotiamine and fenofibrate alone or in a combination decreased nephropathy and endothelial dysfunction in diabetic rats. The lipid profile of these rats, however were normalized only by administration of fenofibrate and not by benfotiamine(77)

6.1.3 In Vitro Studies

Numerous studies have investigated the effect of thiamine and/or benfotiamine on mechanisms associated with the pathogenesis of hyperglycaemia induced damage in vitro. Cultivation of erythrocytes in hyperglycaemia with addition of thiamine enhanced the activity of Transketolase enzyme, lowered production of triose phosphates and methyl-glyoxal and improved concentrations of sedoheptulose-7-phosphate and ribose-5-phosphate(78). Thiamine as well as Benfotiamine have been shown to correct faulty replication of human umbilical vein endothelial cells (HUVEC) and to lower their production of AGEs caused by hyperglycaemia(79). Thiamine also inhibited markers of endothelial cell dysfunction (supressed cell migration and improved von Willebrand factor secretion) caused by hyperglycaemia in bovine aortic endothelial cells(80). Addition of both benfotiamine and thiamine reduced activation of polyol pathway (aldose reductase mRNA expression, enzyme activity and intracellular levels of sorbitol) while increasing expression and activity of TKT in HUVEC and bovine retinal pericytes cultured in hyperglycemia[32]. Notably,

benfotiamine restored impairment of endothelial progenitor cells differentiation caused by hyperglycemia[33]. Possible benfotiamine antioxidant properties and protective effect on DNA have also been investigated. Benfotiamine prevented oxidative stress (probably through direct antioxidant effect) and also DNA damage[34]. The same study also confirmed that benfotiamine increased TKT expression and activity. Intermittent exposure of human retinal pericytes to fluctuating glucose levels induced their apoptosis, the effect was however prevented by thiamine and benfotiamine[35]. It has also been studied whether thiamine and/or benfotiamine affect glucose and lipid metabolism in human skeletal
muscle cells. Benfotiamine but not thiamine increased glucose oxidation while lipid oxidation and metabolism was influenced by neither of the two. Benfotiamine also down regulated NADPH-oxidase-4 expression [36].

Rationale for the choice of cases and controls

The studies done in the past for measurements of thiamine levels had compared diabetic outpatients with normal age matched volunteers(9,13) and shown a significant decrease in thiamine levels among diabetic patients. With evidence of improved healing of ischemic toe-necrosis in animal models on treatment with thiamine derivatives(12), the role of thiamine in development of foot ulcers in diabetic patients needed to be explored further. This was the first study in our country which compared thiamine levels in patients undergoing a lower extremity amputation (cases), with non-amputated diabetics (controls).

MATERIALS AND METHODOLOGY

Materials and Methodology

Source of Data:

The study was conducted in the in-patient wards of Department of General Surgery, Christian Medical College, a tertiary care centre in Vellore, Tamil Nadu. This institute was established in the year 1990 and is now a 2700 bedded multi-specialty hospital. The annual out-patients and in-patients handled were around 2.4 million and 140,000 respectively. The diabetic patients who underwent lower extremity amputations were recruited as cases and the patients who had not undergone amputations were recruited as controls

Key Criteria

Inclusion Criteria

1. For cases
    a. Type II Diabetes Mellitus for more than 5 years
    b. Age more than 30 years
2. For Controls
    a. Type II Diabetes Mellitus more than 5 years
    b. Age more than 30 years
3. Common inclusion: Individuals agreeing to participate in the study with written informed consent.

Exclusion Criteria

1. Alcohol consumption of more than 50 units per week
2. End stage renal disease
3. Individuals who are already receiving thiamine supplements.

Methods

A hospital based prospective case control study was done among the patients in the wards of the general surgical units. The cases were patients with diabetes mellitus, who were undergoing lower extremity amputations. The controls were patients in the wards of the general surgical units with diabetes mellitus who were otherwise healthy and did not undergo a lower extremity amputation. A one-on-one interview was conducted using a questionnaire detailing the patient demographics, anthropometrics and neurological examination. A blood sample was collected, using standard precautions, for measurement of Erythrocyte transketolase Activity, and the values were recorded in the data collection sheet.

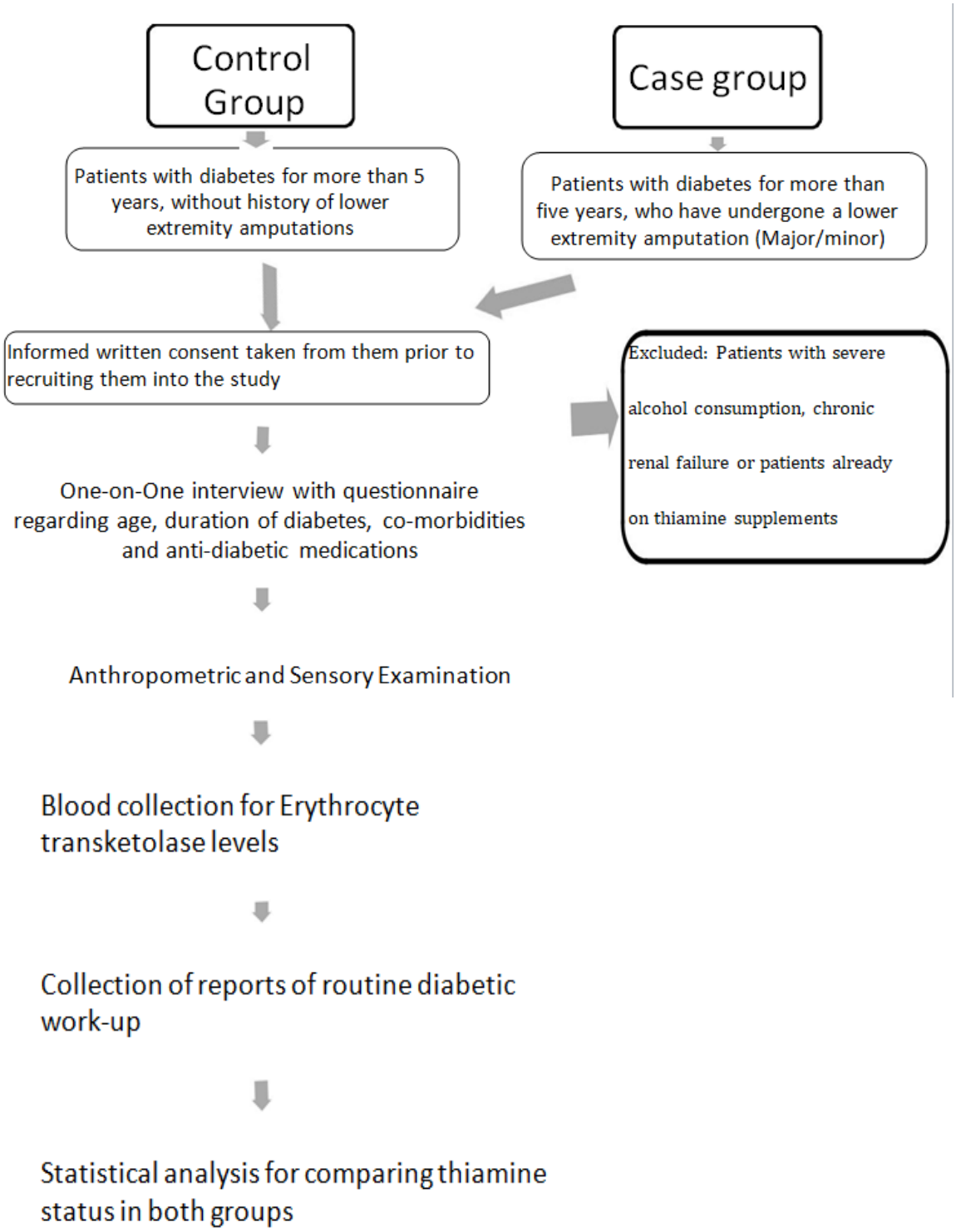
The routine investigations done for diabetic work-up were collected from the hospital medical records system and recorded in the data collection sheet.

A sensory examination of the lower extremities was conducted for evaluation of neuropathy. This examination scored the individual based on the Neuropathy Disability Score which involved assessment of vibration perception threshold using a 128Hz tuning fork over the big toe, temperature sensation by placing a beaker of ice over the dorsum of foot and cutaneous pressure perception assessment using a Semmes-Weinstein monofilament followed by examination of the ankle reflex assessment. The individual would be scored on the basis of the Neuropathy Disability Score and classified as significant neuropathy (score of more than 6 on 10) or insignificant neuropathy (score of less than 6 on 10). For patients with trans-femoral or trans-tibial unilateral amputations, NDS was assessed in the contra lateral foot and the score was then doubled for statistical analysis.

Outcomes

The primary outcome studied was the difference between erythrocyte transketolase levels between the cases and controls. The secondary outcomes studied were the correlation of low

transketolase levels in cases with markers of glycaemic control of the patient and degree of neuropathy.



Sample size:

The sample size was calculated using 'n Master 2.0' software. To test the significant difference between the two groups (primary and secondary outcomes), the minimum required number of cases were approximately 26 in each group. **So the total number of subjects needed for this study was 52.**

Calculation:

$$n = \frac{2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \sigma^2}{(\mu_1 - \mu_2)^2}$$

The variables in the above equation were calculated as below:

Pooled standard deviation (σ) =3.2761

Mean TPPE level in cases, μ_1=16.160%

Mean TPPE level in controls, μ2=13.610%

Standard normal variate for 5% level of significance, $Z_{1-\alpha/2}$ = 1.96

Standard normal variate for 80% power, $Z_{1-\beta}$= 0.84

The mean difference and pooled standard deviation values were taken from the literature: Kursat Dabak T. et al(2012).

Variables

The variables studied were:

1. Demography:
    - Age
    - Gender
2. Details regarding diabetes mellitus
    - Duration of diabetes
    - Type of diabetic treatment whether:
        i. None
        ii. Oral hypoglycaemic drugs only
        iii. Insulin only
        iv. Oral hypoglycaemic drugs and insulin
3. Presence of co-morbid illnesses:
    - Hypertension
    - Ischaemic Heart Disease
    - Dyslipidaemia
4. Anthropometry
    - Height
    - Weight
    - Body Mass Index
5. Type of Amputation among cases
    - Major i.e. trans-tibial or trans-femoral.
    - Minor i.e. ray amputation of digits or trans-metatarsal amputations

6. Modified Neuropathy disability Score
    - Vibration Perception threshold
    - Temperature perception on the dorsum of foot
    - Pin-Prick
    - Achilles Reflex
7. Markers of glycaemic control
    - Fasting Blood Sugar
    - Post-Prandial Blood Sugar
    - Glycosylated Haemoglobin levels(HbA1c)
    - Urinary Micro-albumin
    - Serum Creatinine
8. Thiamine levels calculated as Erythrocyte transketolase levels (a surrogate marker of thiamine status).
    - Since there was no standard value in terms of erythrocyte transketolase activity in literature, the mean value among the control group was taken as the lower limit of normal and the low thiamine status was defined in the case group as subjects having an ETKA below the mean ETKA of the control group.

STATISTICAL ANALYSIS

Statistical Analysis

Data from the case report form was entered into the Epidata v 3.1 data entry software and then exported to SPSS. The analysis was performed by trained biostatisticians

The data was analysed using the STATA I/C 13.1. All demographic and clinical variables were summarised as counts and percentages for categorical variables, mean and standard deviation for symmetrically distributed continuous variables and median and range for skewed continuous variables. Rank sum test was used to compare the categorical variables and Pearson correlation coefficient/Spearman's correlation co-efficient was used for continuous variables.

RESULTS

Results

A total of 58 patients were recruited in this study between February 2016 and September 2017 but only 48 samples were suitable for processing for erythrocyte transketolase activity. There were 24 patients each in the Case and control group respectively. The 'Case' group were patients with diabetes mellitus who underwent a lower extremity amputation and the 'Control' group were patients with diabetes mellitus who had not undergone a lower extremity amputation.

Variables	Case group	Control group	P Value
Age Mean(SD)	54.6(10.9)	54.6(9.9)	0.99
Gender			
Male (%)	16(66.67%)	17(70.83%)	0.755
Female (%)	8(33.33%)	7(29.17)	
Median Duration of Diabetes	8	10	0.96
Type of treatment			
None	2	1	0.551
OHA only	12	14	
Insulin only	5	2	
OHA and Insulin	5	7	
Co-morbidities			
Hypertension(% of total)	7(29.17%)	7(29.17%)	1.000
Ischaemic Heart Disease(% of total)	3(12.5%)	0(0%)	0.074
Dyslipidaemia(% of total)	3(12.5%)	1(4.17%)	0.296

Weight Mean(SD)	68.1(13.4)	67.9(10.2)	0.96
Variables	**Case group**	**Control group**	**P Value**
Height Mean(SD)	161.5(9.48)	163.8(9.62)	0.14
Body Mass Index Mean(SD)	26.4(4.1)	25.4(3.1)	0.31
Fasting blood sugar(median)	176	155	0.58
Post prandial blood sugar(median)	272	241	0.10
HbA1c	9.5	8.9	0.17
Serum Creatinine	0.8	0.9	0.36

Demographic Data

The baseline data comparing the Case group and control group are tabulated below.

- **Gender**

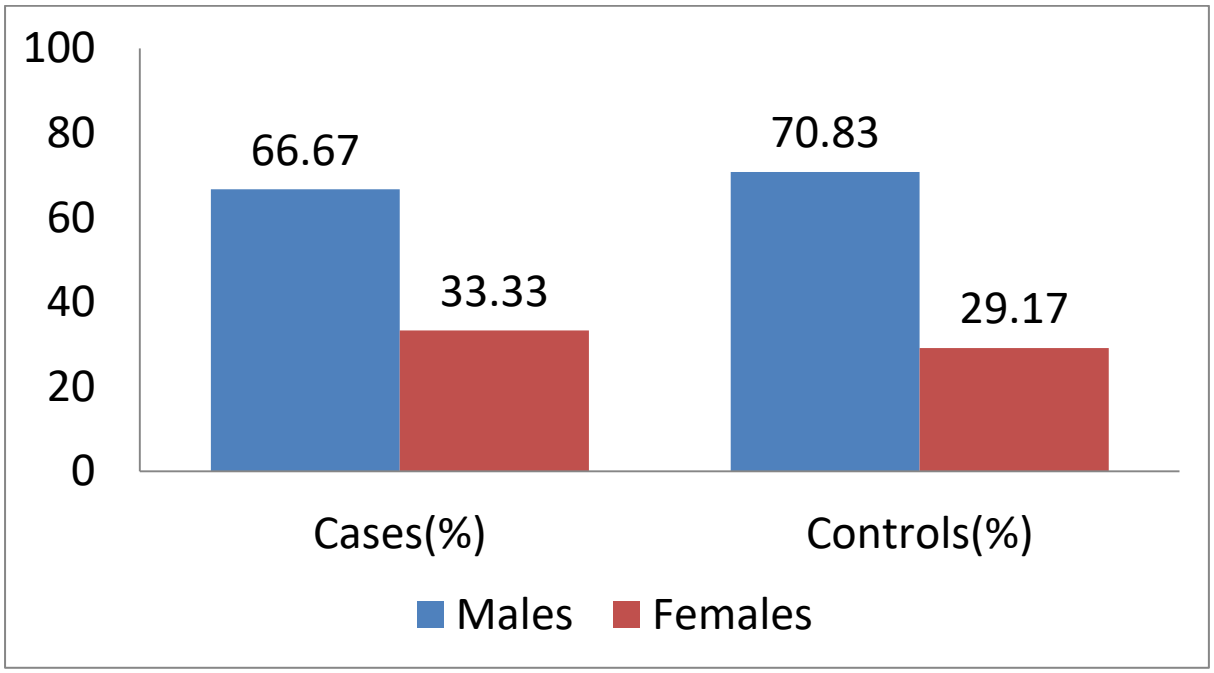
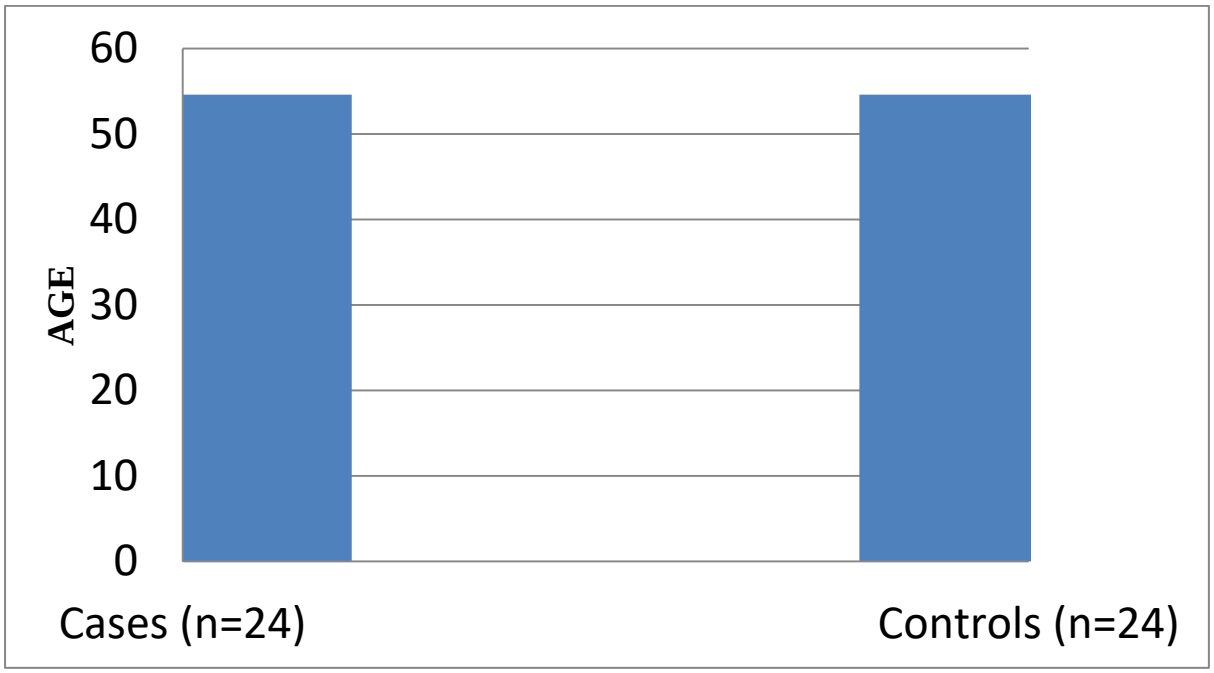


Figure 8 Comparison of Gender Distribution between cases and controls.

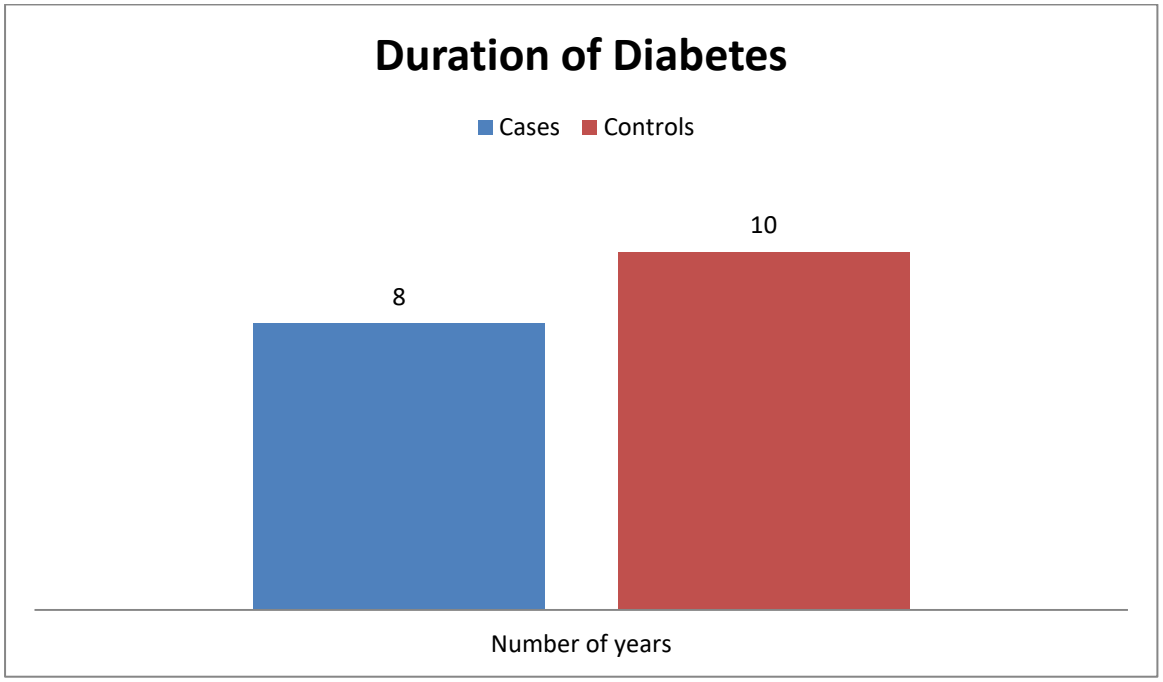
Sixty six percent of patients in the Case group were males and Seventy percent of Control group were males. There was no significant difference in the gender distribution between these two groups.

- **Age**



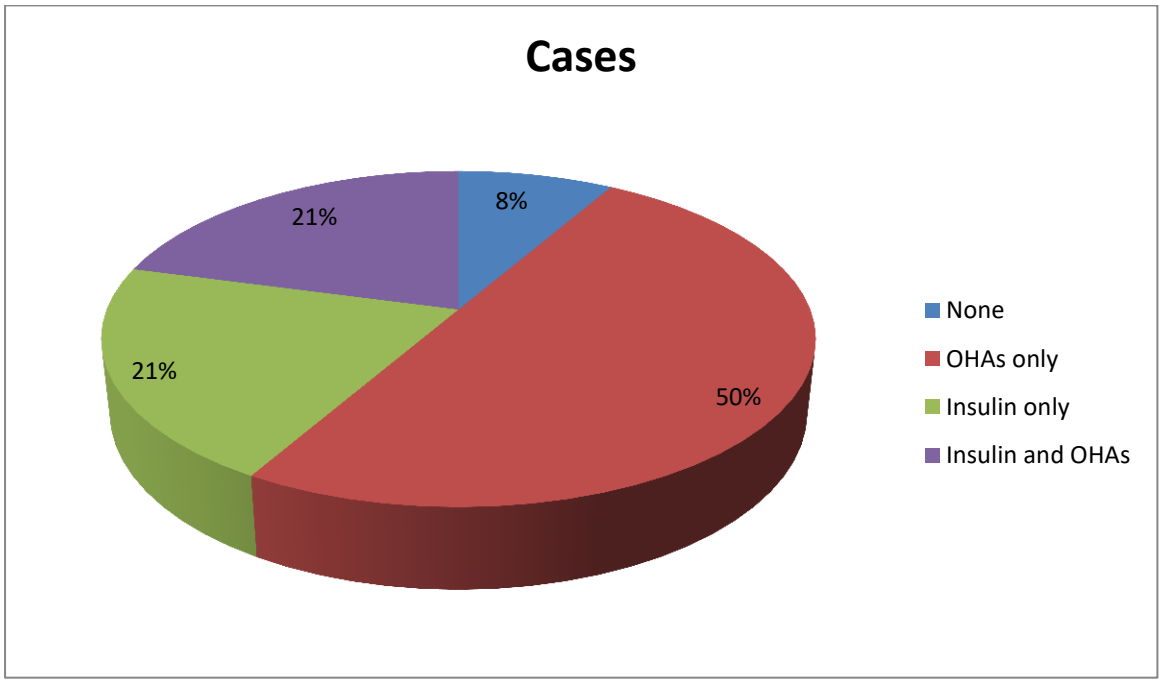
The above histogram shows the mean age of patients in Case group and Control group. The mean ages of patients in both groups were 54.6 years.

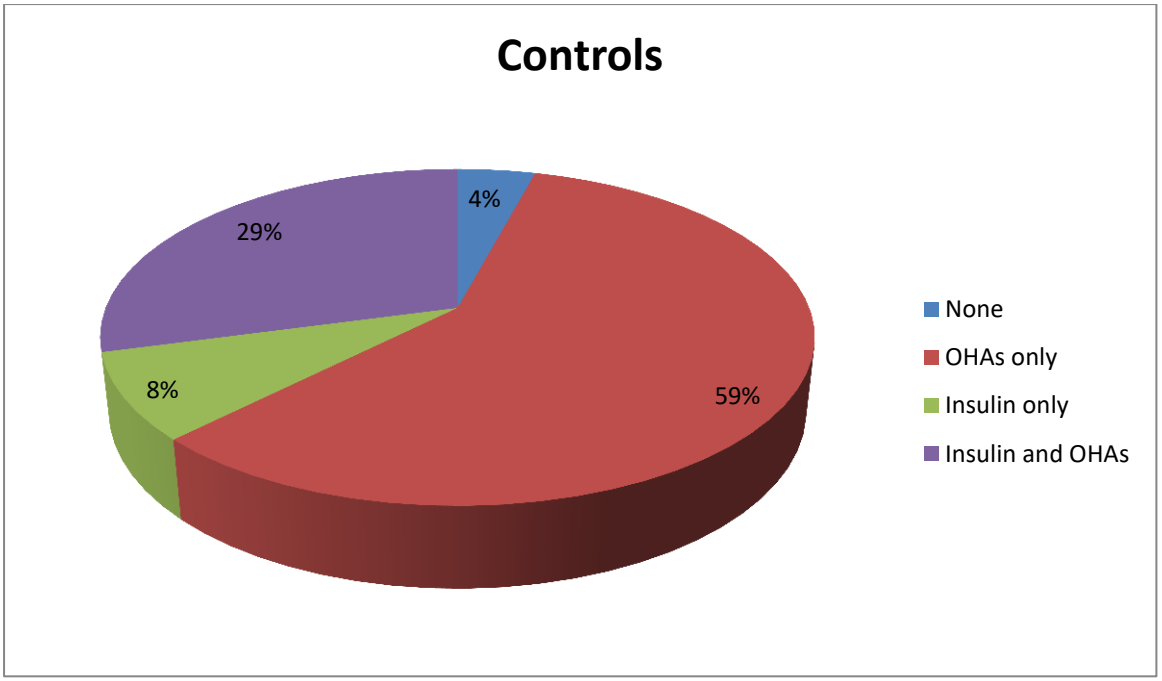
- **Duration of Diabetes**



The above figure describes the median duration of diabetes in the cases and controls. The median duration in the case group was 8 years with minimum duration of 5 years and maximum duration of 16.5 years. . The median duration in the control group was 10 years with minimum duration of 5 years and maximum duration of 17 years.

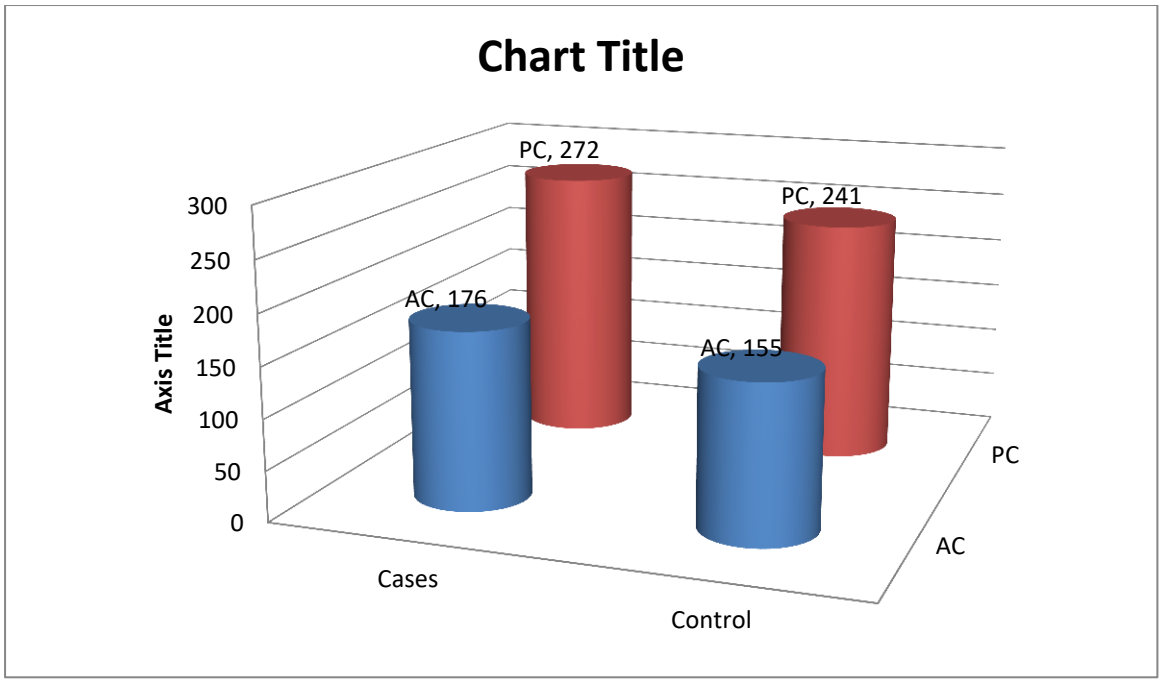
Type of Treatment





The above pie charts display the distribution of treatment taken by patients in the case group and control group. In both the groups the most common modality was oral hypoglycaemic drugs with 50% and 59% in case and control group, respectively

Fasting and post prandial Blood sugars



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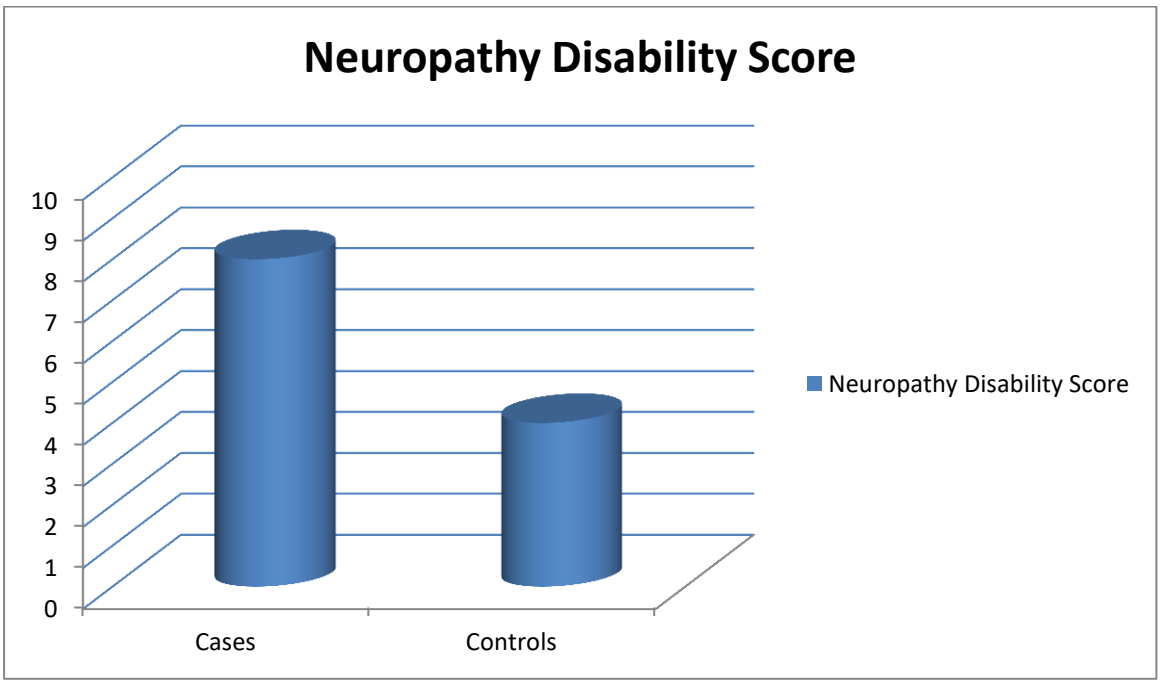
- **Neuropathy Disability Score**



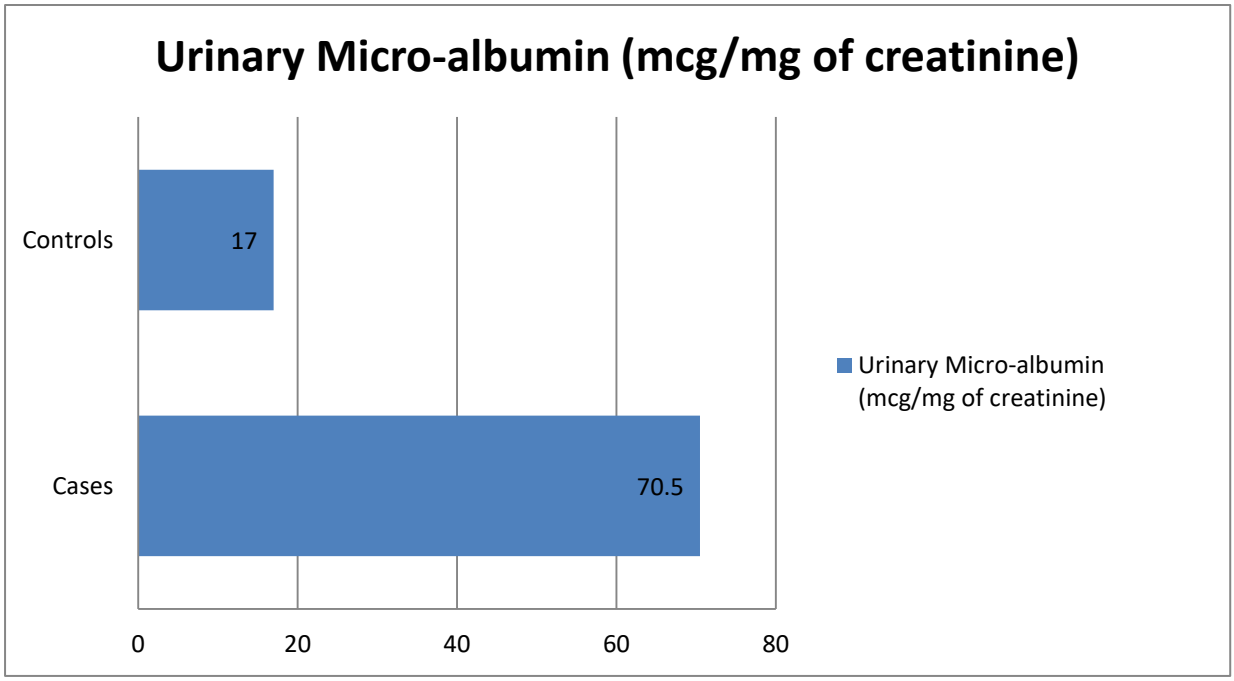
The above clustered histogram shows the comparison of neuropathy disability score in the case and control group. The median score in Case group was 8 and in control group was 4. The difference was statistically significant with p value less than 0.001.

- **Urinary Micro-albumin**

	Normal urinary microalbumin (less than 30mcg/mg creatinine)	Increased Urinary micro-albumin (more than 30mcg/mg creatinine)	P value
Cases	6	18	0.003
Controls	16	8	

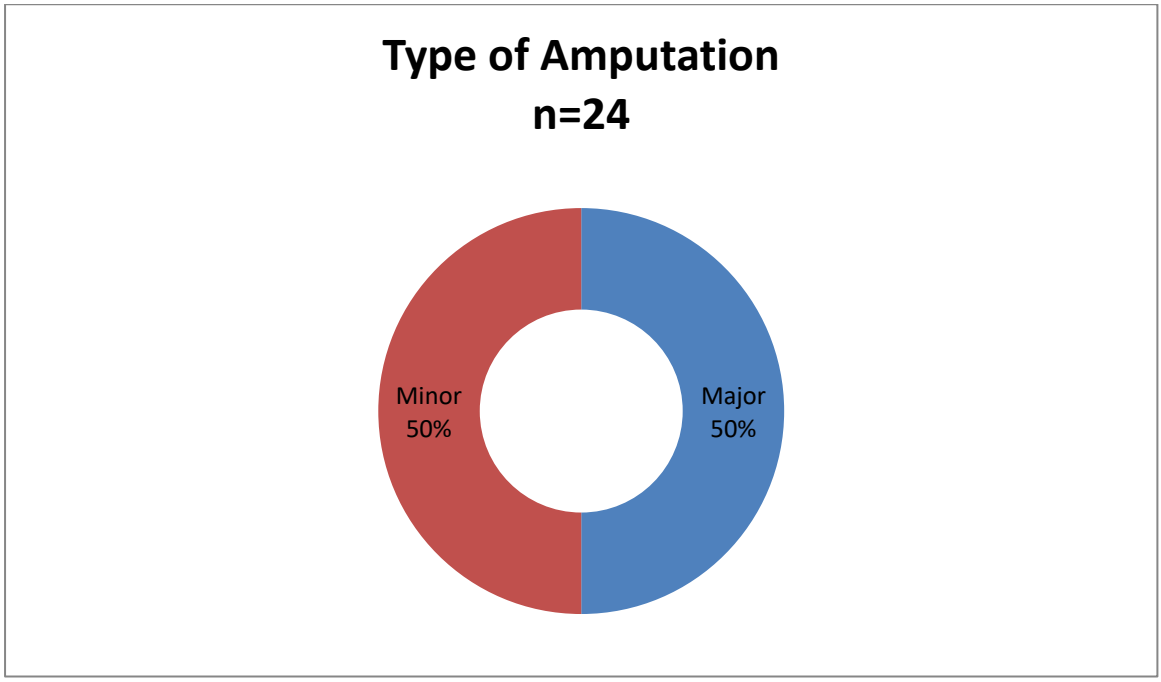
The above table shows the distribution of urinary micro-albumin among cases and controls. Seventy five percent of cases had abnormal urinary micro-albumin levels as compared to

thirty three percent of controls with abnormal urinary micro-albumin levels with the difference being statistically significant (p value = 0.003).



The above bar diagram demonstrates the comparison of urinary micro-albumin levels in the case and control groups. The median urinary micro-albumin excretion among the cases was 70.5mcg/mg of Creatinine as compared to 17mcg/mg of Creatinine in the control group. The difference was statistically significant with p value of 0.001.

Type of Amputation



The above chart shows the distribution of the type of amputation in the case group. 12 out of 24 patients underwent minor amputations including trans-metatarsal and ray amputations. 12 out of 24 patients underwent major amputations including trans-tibial and trans-femoral amputations.

Co-morbid Illnesses

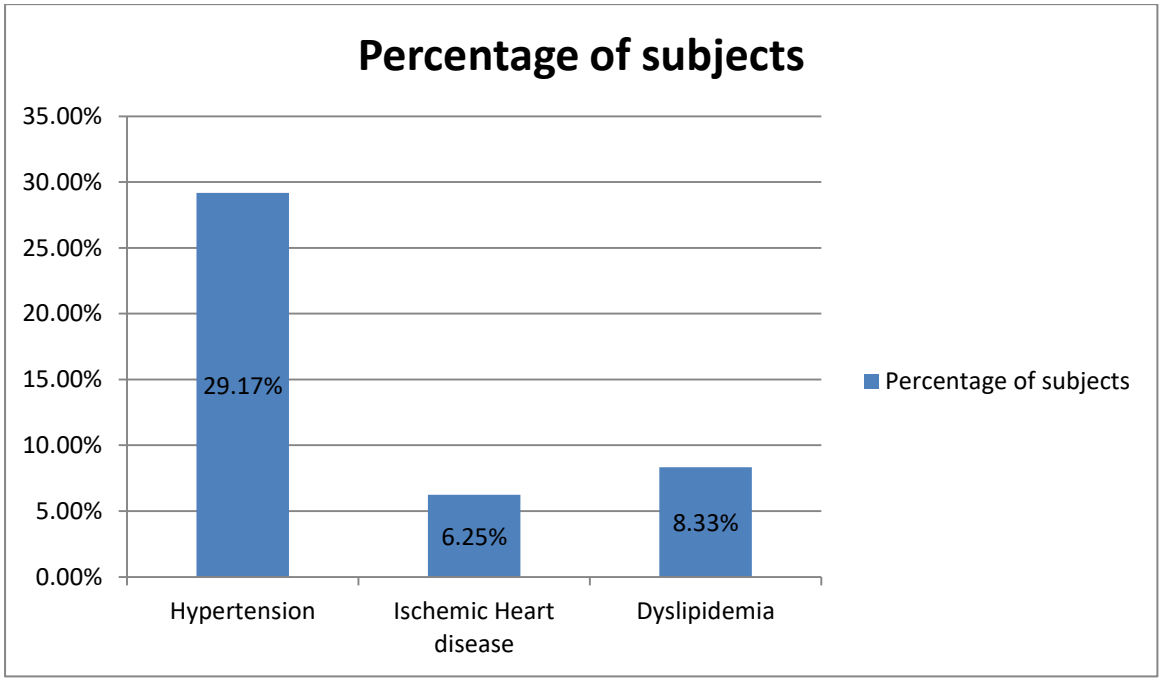


Figure 9 Presence of comorbid conditions among the study subjects

The above chart shows the distribution of co-morbid conditions among the subjects in the study. Hypertension (29.17%) was the most common co-morbid condition noted among the study subjects with 7 cases and 7 controls having hypertension.

Erythrocyte trans-ketolase Activity

Table 3 Comparison of erythrocyte transketolase activity among cases and controls.

	No. of Subjects	Mean ETKA	Standard deviation	Median	P - value
Cases	24	78.18	22.45	78.33	0.7997
Controls	24	83.75	23.10	78.30	

The above table compares the erythrocyte transketolase activity (ETKA) between the case and the control group. The values were reported as concentration of enzyme $x10^{-3}$ Nano gram

per Nano gram of protein. The mean ETKA in the case group was 78.18 x 10^{-3} ng/ng whereas the mean ETKA in the control group was 83.75 x 10^{-3} ng/ng. The median value in both groups was nearly similar with 78.33 x 10^{-3} ng/ng in the case group and 78.30 x 10^{-3} ng/ng in the control group. Since there was no standard value in terms of erythrocyte transketolase activity in literature, the mean value among the control group (83.75 x 10^{-3} ng/ng) was taken as the lower limit of normal and the low thiamine status was defined in the case group as subjects having an ETKA below the mean ETKA of the control group.

Thiamine status in Cases

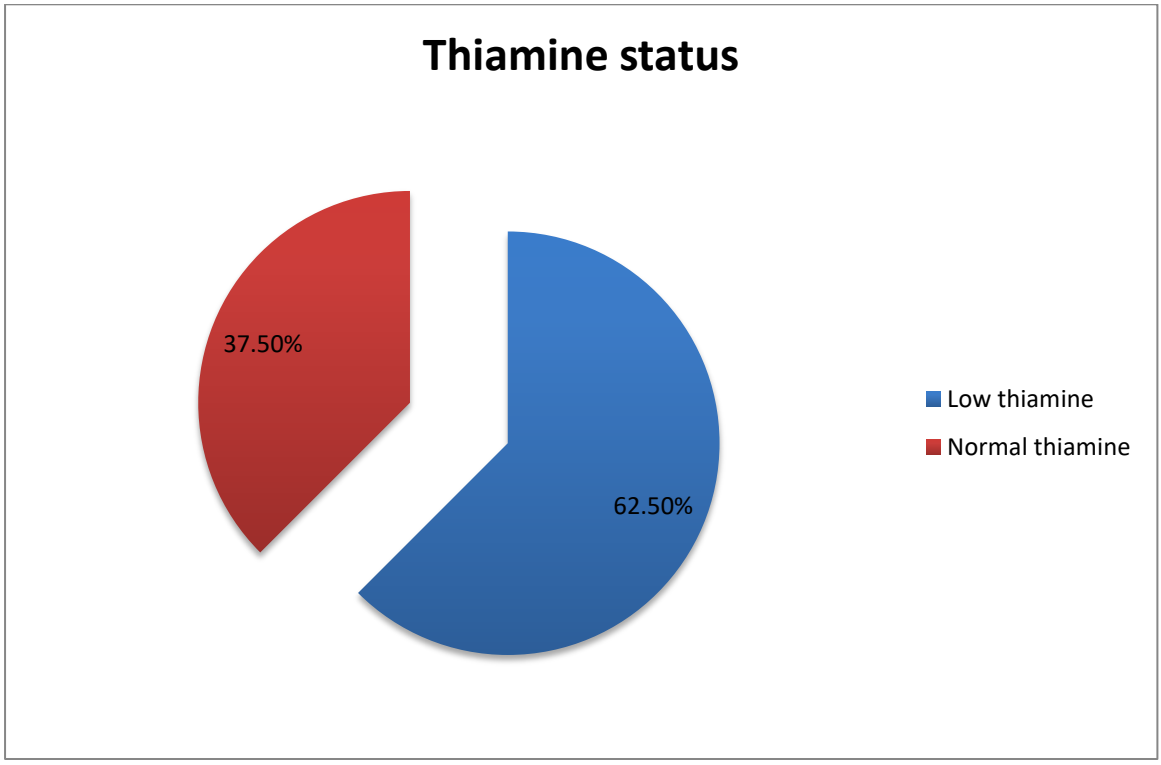


Figure 10 Distribution of low thiamine among cases.

The above pie chart depicts the distribution of low thiamine levels among the cases. Sixty two percent of the patients in the case group had low thiamine levels as compared to the thirty seven percent of patients who had a normal thiamine levels.

	Low thiamine	Percentage
Males	8	50%
Females	7	87.5%

The above table shows the distribution of low thiamine levels among the cases. Fifty percent of the male patients had low thiamine levels whereas eighty seven percent of the females had low thiamine levels.

Modified Neuropathy Disability Score

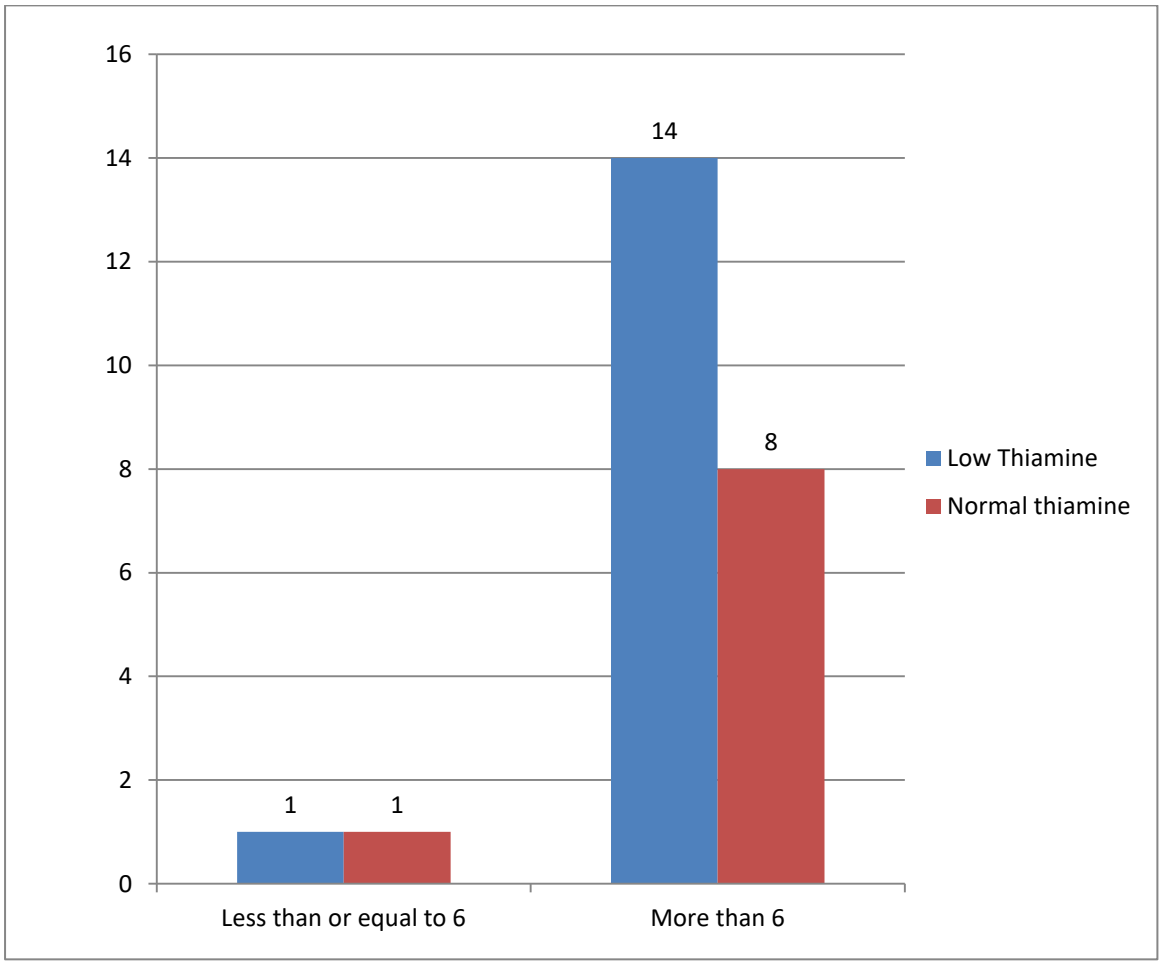


Figure 11 Distribution of Low thiamine levels among cases with normal and high neuropathy disability score.

The above histogram describes the distribution of low thiamine levels with respect to the neuropathy disability score. A score of more than 6 is predictive of foot ulceration and subsequent amputation. Among the cases with high neuropathy disability score (i.e. >6) 14 subjects had low thiamine levels and 8 subjects had normal thiamine levels. One subject each with normal NDS had low and normal thiamine levels. The correlation with thiamine and neuropathy disability score was not significant with p value being 0.703.

Type of Amputations

Table 4 Table with distribution of low thiamine levels in different categories of amputations

Type of Amputation	Low thiamine	Normal thiamine	P Value
Major	9	3	0.206
Minor	6	6	

The above table describes the distribution of low thiamine levels in cases undergoing major and minor lower extremity amputations. Nine out of twelve cases who underwent major (Trans-tibial or trans-femoral) amputations had low thiamine levels as compared to six out of 12 patients with minor amputations who had low thiamine levels. But the difference between the two groups was not statistically significant with p value of 0.206.

Age and low thiamine status

Age	Low thiamine	Normal thiamine
Less than 40 years	1	0
More than 40 years	14	9

The above table describes the distribution of low thiamine levels in cases with respect to their age. Fourteen subjects (62.5%) in the case group who were above 40 years of age and had low thiamine as compared to 9 cases with normal thiamine levels above 40 years of age. The above difference was not statistically significant with p value of 0.429.

Duration of diabetes

Duration of diabetes	Low thiamine	Normal thiamine	P Value
Less than 10 years	8	5	0.916
More than 10 years	7	4	

The above table describes the distribution of low thiamine in the cases with respect to the duration of diabetes. Eight cases having diabetes less than 10 years had low thiamine as compared to 7 cases with diabetes more than 10 years. There was no statistical difference among these two groups (P value = 0.916).

Mode of Diabetic Treatment and thiamine status

Type of Treatment	Low thiamine	Normal thiamine	P Value
No treatment	1	1	0.703
Any treatment	14	8	

Type of Treatment	Low thiamine	Normal thiamine	P value
Only OHA	11	8	0.364
Only Insulin	4	1	

The above two tables depict the distribution of low thiamine status in cases with respect to the type of diabetic treatment taken by the cases. Fifty percent of patients, who were

not on any anti-diabetic treatment, had low thiamine levels whereas sixty four percent of patients on any form of anti-diabetic treatment (oral hypoglycaemic agents, insulin or both) had low thiamine levels. There was no significant difference among these two groups (P value= 0.703). Among cases taking anti-diabetic treatment, low thiamine was seen in eleven out of 19 patients on oral hypoglycaemic agents whereas four out of five patients taking insulin had low thiamine levels. There was no significant difference in these two treatment modalities with respect to thiamine status (P value= 0.364).

Body mass index and thiamine status

Body Mass Index (BMI)	Low thiamine	Normal Thiamine	P Value
Less than 25	5	3	1.000
More than 25	10	6	

The above table shows the distribution of body mass index and thiamine status. Sixty two percent of cases (5 out of 8) with body mass index less than 25, had low thiamine levels and similarly sixty two percent of cases with body mass index higher than 25 had low thiamine levels. There was no difference among these groups with respect to thiamine levels (P value = 1.000).

Glycosylated haemoglobin percentage and thiamine status

HbA1c (%)	Low thiamine	Normal thiamine	P value
Less than 8	4	4	0.371
More than 8	11	5	

The above table describes the distribution of low thiamine levels with respect to the percentage of glycosylated haemoglobin (HbA1c) in the blood. Fifty percent of cases (4 out of 8) with HbA1c less than 8% had low thiamine levels whereas sixty nine percent of cases with HbA1c more than 8 (describing poor glycaemic control) had low thiamine levels. The difference among these groups was not statistically significant (P value= 0.371).

Urinary Micro-albuminuria and thiamine status

Urinary Micro-albumin (mcg/mg of Creatinine)	Low thiamine	Normal thiamine	P Value
Less than 30	2	3	0.243
More than 30	13	6	

The above table describes the distribution of low thiamine levels and urinary micro-albumin. Only forty percent of cases (2 out of 5) with normal urinary micro-albumin levels had low thiamine whereas sixty eight percent of cases (13 out of 19) with abnormal urinary micro-albumin levels had low thiamine levels. This difference was not statistically significant (P value = 0.243)

Age and type of amputation

Age (years)	Major amputation	Minor Amputation	P value
Less than 40	1	0	0.307
More than 40	11	12	

The above table shows the comparison of type of amputation with respect to age among the cases. Ninety two percent of cases (11 out of 12) who had undergone a major amputation were more than forty years of age whereas all cases who had undergone minor amputations were more than 40 years of age. The difference was not statistically significant (P value = 0.307).

Duration of diabetes and type of amputation

Duration of diabetes (years)	Major amputation	Minor Amputation	P value
Less than 10	7	6	0.682
More than 10	5	6	

Then above table displays the distribution of type of amputation with respect to the duration of diabetes. Fifty eight percent of cases who had undergone major amputations (7 out of 12) had diabetes for less than 10 years whereas the duration of diabetes was

evenly distributed in the cases that had undergone minor amputations. There was no statistical significance between these groups (P value = 0.682).

Anti-diabetic Treatment and the type of amputation

Type of Treatment	Major Amputation	Minor Amputation	P Value
No treatment	1	1	1.000
Any treatment	11	11	

Type of Treatment	Major Amputation	Minor Amputation	P value
Only OHAs	10	9	0.615
Only Insulin	2	3	

The above two tables display the distribution of the type of amputation with respect to the mode of anti-diabetic treatment. The type of amputation was evenly distributed among cases with and without diabetic treatment. Among the cases undergoing anti-diabetic treatment, fifty two percent of cases (10 out of 19) on oral hypoglycemic drugs had a major amputation whereas forty percent of cases on insulin only (2 out of 5) had a major amputation. The difference in these groups was not statistically significant as depicted by the P values in the table.

Body mass index and type of amputation

Body Mass index	Major Amputation	Minor Amputation	P Value
Less than 25	5	3	0.386
More than 25	7	9	

The above table displays the distribution of type of amputations with respect to the body mass index of the cases. Fifty eight percent of the cases (7 out of 12) who underwent a major amputation had a body mass index of more than 25 whereas seventy five percent of the cases (9 out of 12) who underwent minor amputations had a body mass index of more than 25. This difference was not statistically significant (P value= 0.386).

Glycosylated haemoglobin percentage and type of amputation

HbA1c (%)	Major amputation	Minor Amputation	P Value
Less than 8	4	4	1.000
8 or more	8	8	

The above table depicts the distribution of the type of amputation with respect to the glycaemic control of the patient. Equal number of patients undergoing major and minor amputations had glycosylated haemoglobin percentage less than eight and more than eight.

Urinary Micro-albumin and type of amputation

Urinary Micro-albumin (mcg/mg of Creatinine)	Major Amputation	Minor Amputation	P value
Less than 30	1	4	0.132
More than 30	11	8	

The above table shows the distribution of major and minor amputations among cases with respect to the presence or absence of urinary micro-albinuria. Ninety two percent of cases who underwent major amputations (11 out of 12) had urinary micro-albuminuria whereas only sixty seven percent of cases (8 out of 12) who underwent minor amputations had abnormal urinary micro-albumin levels. This difference was however not statistically significant. (P value= 0.132)

DISCUSSION

Discussion

A hospital based prospective case control study was done to include a total of 48 patients. The variables in the demographic and anthropometric data such as age, sex, patient weight, height, body mass index, duration of diabetes were equally distributed between the two groups of 24 patients each and were hence, comparable. Both the groups were similar with respect to their prevalence of co-morbid illnesses.

In terms of erythrocyte transketolase levels, the mean value in the case arm was 78.18 $x10^{-3}$ ng/ng whereas the mean erythrocyte transketolase levels in the control arm was 83.75$x10^{-3}$ ng/ng but the difference was not statistically significant. A study done by Kursat Dabak T and his colleagues comparing thiamine levels among normal individuals, diabetics without foot lesions and diabetes with foot lesions, had given similar results(84). Multiple studies have shown low thiamine levels among diabetic individuals as compared to healthy controls, but none had compared the thiamine levels among diabetic patients with or without lower extremity amputations(9,10,13). The mean value among the controls (83.75$x10^{-3}$ ng/ng) was considered as the lower limit of normal thiamine levels. With that assumption, sixty two percent of the cases had low thiamine levels.

Low thiamine levels were analysed in the case group and compared to the demographic and anthropometric variables. Sixty two percent of cases above the age of forty had low thiamine levels. There was no significant correlation of low thiamine status with duration of diabetes (p value=0.916), mode of treatment (p value=0.703) or body mass index (p value=1.00).

Low thiamine levels were analysed in the case group and compared to the markers of glycaemic control. There was no significant association of low thiamine status with glycosylated haemoglobin percentage more than 8% (p value=0.371) or urinary micro-albuminuria (p value=0.243).

The median neuropathy disability score among cases was 8 as compared to 4 in the control group and the difference was statistically significant with p value of less than 0.001. This was in agreement with the findings of 'The North-West Diabetes Foot Care Study' which reported that Neuropathy disability score more than 6 was associated with significant risk of foot ulceration and subsequent amputation in diabetics(23).

The median urinary micro-albumin among the cases was 70.5mcg/mg of creatinine as compared to17mcg/mg of creatinine in the control arm and the difference was statistically significant with p value of 0.001. A study published in the Indian journal of Nephrology deduced a prevalence of micro-albuminuria to be 14.2%(83). However in our current study, fifty four percent of recruited patients had urinary micro-albuminuria. Among the cases, 75% of patients had micro-albuminuria whereas only 33 percent of patients in the control arm had micro-albuminuria and the difference was statistically significant with p value of 0.003.

Among the various components of metabolic syndrome, hypertension was noted to be the most common co-morbid condition among the subjects with twenty nine percent of the patients having hypertension.

Longer duration of diabetes has been noted to be an independent risk factor of micro-vascular and macro-vascular complications of diabetes(81). The median duration of diabetes in the case group was more (10 years) as compared to the control group (8 years) which was in agreement to the aforementioned study but the difference was not statistically significant.

Oral hypoglycaemic agents were noted to be the most common form of anti-diabetic treatment among cases and controls. Elevated Fasting and post prandial blood sugars have been associated with macro-vascular complications and cardiovascular disease associated

with diabetes mellitus(82). In this study, the median fasting and post prandial blood sugars were higher in the case group as compared to the control group (cases- 176 and 272mg/dl and controls 155 and 241mg/dl) but the difference was not statistically significant.

CONCLUSION

The mean erythrocyte transketolase levels measured among the cases were lower than that for the control group but the difference was not statistically significant. Low thiamine levels were identified by using the mean value of the control arm as the lower limit of normal erythrocyte transketolase level. Using this value, sixty two percent of the cases were identified to have low thiamine levels. The low thiamine levels did not show any significant association with age, gender, body mass index or mode of diabetic treatment.

The low thiamine levels were also compared to markers of glycaemic control and level of neuropathy among the cases. However, there was no significant correlation between the low thiamine levels and HbA1c, urinary micro-albumin and modified neuropathy disability score. Interestingly, the median neuropathy score among the cases (NDS=8) was significantly higher than that in the control arm (NDS=4). This was an important finding since a score of six or more was predictive of foot ulceration and subsequent risk of amputation, in the precious limb of the patients who had already undergone amputations of the contra-lateral limbs. Also the median urinary micro-albumin among the cases (urine micro-albumin=70.5mg/mg of creatinine) was significantly higher than that among the controls (urine micro-albumin=17mg/mg of creatinine). The prevalence of abnormal urinary micro-albumin, suggestive of incipient diabetic nephropathy, was significantly high among cases (75%) as compared to the controls (33.3%).

In view of the above, it is imperative that further role of thiamine should be investigated to establish a correlation between thiamine deficiency and complications of diabetes mellitus.

LIMITATION

The sample size calculated was 52 including 26 subjects in each arm. Despite recruiting 58 patients, only 48 samples were suitable for analysis of erythrocyte transketolase levels with 24 patients in each arm.

Thiamine supplementation may have confounded the correlation between thiamine/ETKA levels and other parameters that were studied.

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ANNEXURES

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

April 14, 2016

Dr. Binoy Abraham,
PG Registrar,
Department of Surgery - 1,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research grant project NEW PROPOSAL:**
Comparison of thiamine status in type II diabetes mellitus with and without lower extremity amputations : A prospective case control study.
Dr. Binoy Abraham (Employment Number: 29346), PG Registrar, Surgery I, Dr. John C. Muthusami (Employment Number: 12899), Surgery, Dr. Pranay Gaikwad (Employment Number: 31224), General Surgery, Mr. Arun Jose, Clinical Biochemistry

Ref: IRB Min No: 9788 [OBSERVE] dated 03.12.2015

Dear Dr. Binoy Abraham,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George,
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. John C. Muthusami, Dept. of Surgery, CMC

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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April 14, 2016

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Ref: IRB Min No: 9788 [OBSERVE] dated 03.12.2015

Dear Dr. Binoy Abraham,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Comparison of thiamine status in type II diabetes mellitus with and without lower extremity amputations : A prospective case control study" on December 03rd 2015.

The Committee reviewed the following documents:

1. IRB Application format
2. Data Collection Sheet
3. Patient Information Sheet (English, Tamil, , Bengali, Hindi, Telugu)
4. Cvs of Drs. Binoy Abraham, John C. Muthusami, Pranay Gaikwad, Mr. Arun Jose.
5. No. of documents 1 – 4

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on December 03rd 2015 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP (Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson(Research Chairperson), Member Secretary (Ethics Committee), IRB. CMC, Vellore	Internal, Clinician
Dr. RV. Shaji		Professor, Heamatology, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS, MCh	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Rajesh Kannangai	MD, PhD.	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Comm IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, CMC, V	External, Scientist &Epidem
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgica Nursing, CMC, Vellore	Internal, Nurse
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Comn Health, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Comparison of thiamine status in type II diabetes mellitus with and without lower extremity amputations : A prospective case control study" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

Fluid Grant Allocation:
A sum of 1,00,000/- INR (Rupees One Lakh Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an Ist Installment. The rest of the 50,000/- INR (Rupees Fifty Thousand only) each will be released at the end of the first year as 2 nd Installment

Yours sincerely

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min No: 9788 [OBSERVE] dated 03.12.2015

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	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
1	subject	name	hospno	age	durdm	dmtreat	htn	ihd	dyslip	alcohol	thiamine	height	weight	bmi	amputation	neuroscore	fasting	postpran	hbalc	urinemicro	serum	erythro	sex
2	1	ELANGOVAN K.	520423g	51	5	1	2	2	2	0	2	155	57	23.7	2	8	135	100	11.4	100	0.61	72.9	1
3	1	SAMPARTHI CHETTY P.	243361d	73	25	4	2	2	2	0	2	160	66	25.8	2	8	271	277	7.7	50	0.67	78.33	1
4	1	JAYARAMAN	979001f	59	6	2	2	2	2	0	2	160	75	29.3	2	10	88	327	11.1	105	1.19	100	1
5	1	MD.HANIF MOLLA	719369G	55	5	2	2	2	2	0	2	174	88	29.11	2	8	236	371	11.1	12	1.11	78.33	1
6	2	HARI NARAYAN PODDAR	726806G	47	10	2	2	2	2	0	2	180	96	29.6	3	2	224	194	6.4	5	0.7	70	1
7	2	GRACE PATHIMA	883132A	64	26	4	1	2	1	0	2	164	73	27.1	3	2	69	107	6.1	3	0.93	51.7	2
8	1	RAMESH KUNDU	539763G	65	22	4	2	2	2	0	2	164	80	29.7	1	8	177	204	8.7	91	0.74	74.3	1
9	2	DIPAN KR DHAR	758743G	57	15	2	2	2	2	4	2	158	60	24	3	2	154	200	6.7	39	1.05	78.3	2
10	1	ANAND SARKAR	771510G	42	5	2	2	2	2	0	2	164	70	26	1	10	88	67	7.8	30	0.84	75	1
11	2	ITTAN P.V.	406496G	77	6	2	2	2	2	0	2	164	74	27.5	3	2	147	129	6.4	7	1.04	65	1
12	2	JEELA S.	505788G	45	5	2	2	2	2	0	2	170	76	26.3	3	2	207	336	10.9	9	0.67	83.3	2
13	1	DULAL DAS	772719G	35	6	2	2	2	2	0	2	166	88	31.9	1	8	168	200	10	226	0.62	61.7	1
14	2	MD SHAMSUR RAHMAN	838745G	52	16	4	1	2	2	0	2	174	67	22.1	3	2	383	319	10.4	400	1.1	61.66	1
15	2	PRABIR KUMAR KHAN	854691G	68	10	3	2	2	2	0	2	156	56	23	3	2	157	247	6.5	40	0.88	67.5	1
16	2	BABY PAUL	696550G	60	10	4	1	2	2	0	2	140	45	23	3	3	67	265	6	16	0.63	141.7	1
17	1	PUNITHA V.	559792G	55	6	3	1	2	2	0	2	154	80	33.7	2	8	141	669	12.4	400	0.59	41.8	2
18	1	VICTORIA A.	982016D	51	15	2	1	2	2	0	2	152	77	33.3	2	10	176	300	10.4	162	1.01	46	2
19	1	SELVARAJ	561499G	85	15	4	2	1	2	0	2	184	94	27.8	1	10	191	195	7.7	85	1.24	96.6	1
20	2	BABU NAIDU P.	561184g	45	10	2	2	2	2	0	2	178	72	22.7	3	6	101	195	11.7	13	0.69	86.6	1
21	2	GANASUNDAR S.	874990G	49	5	2	2	2	2	0	2	164	60	23.8	3	2	124	144	10	23	0.87	98.3	1
22	2	THAHERA M.	617247G	55	5	4	2	2	2	0	2	155	75	31.2	3	8	226	356	9.9	8	0.66	68.6	2
23	2	ALAUDDIN ANSARI	795912G	44	10	2	2	2	2	0	2	167	63	22.6	3	4	139	248	9.1	15	0.76	88.33	1
24	2	PRAKASH KUMAR SINGH	524649G	47	5	2	2	2	2	0	2	162	67	25.5	3	4	87	128	6.2	6	0.88	143.3	1
25	1	KASINATHAN.B	071997D	61	21	4	2	2	2	0	2	162	50	19.1	2	10	202	426	11.4	149	1.42	101.4	1
26	2	VIJAYAKUMAR	401575B	53	20	2	2	2	2	0	2	170	83	28.7	3	4	104	177	7.4	3	0.76	107	1
27	1	RAGHAVAN.P	061735A	53	20	3	1	2	2	0	2	154	80	33.7	2	10	385	414	14.6	68	1.02	81.4	1
28	1	SRIPATHAM.S	563503B	53	15	2	2	2	2	0	2	174	80	26.4	2	8	309	362	11.4	42	0.8	86	1

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
1	subject	name	hospno	age	durdm	dmtreat	htn	ihd	dyslip	alcohol	thiamine	height	weight	bmi	amputation	neuroscore	fasting	postpran	hbalc	urinemicro	serum	erythro	sex
26	2	VIJAYAKUMAR	401575B	53	20	2	2	2	2	0	2	170	83	28.7	3	4	104	177	7.4	3	0.76	107	1
27	1	RAGHAVAN.P	061735A	53	20	3	1	2	2	0	2	154	80	33.7	2	10	385	414	14.6	68	1.02	81.4	1
28	1	SRIPATHAM.S	563503B	53	15	2	2	2	2	0	2	174	80	26.4	2	8	309	362	11.4	42	0.8	86	1
29	2	SUBRAMANI	514361G	69	5	2	1	2	2	0	2	160	74	28.9	3	6	226	271	8.9	18	1.34	97.1	1
30	1	ERUKALA LALITHAMMA	562663G	48	8	2	2	2	2	0	2	158	64	25.6	1	10	100	151	10.1	25	0.54	74.3	2
31	2	ANTHAIA R C	562599G	77	18	4	1	2	2	0	2	172	70	24.2	3	8	217	361	9.2	38	1.16	71.4	2
32	2	SATHYA R	566073G	48	18	2	2	2	2	0	2	160	60	23.4	3	8	243	243	13.4	27	0.61	72	2
33	1	MANICKAMMAL P.	203842G	62	5	2	2	2	2	0	2	150	60	26.7	1	10	106	149	11.5	158	0.77	56.7	2
34	1	NILATHTHAANDAN .M	564805G	48	15	4	2	2	2	0	2	158	48	23.2	1	10	279	515	8.8	73	0.67	80	1
35	2	ROSY J	561882G	52	25	4	2	2	2	0	2	158	58	23.2	3	6	160	240	8.2	40	0.82	95	2
36	1	BALAJI R	564375G	58	5	2	1	1	1	0	2	180	60	23.2	1	10	184	293	9.2	67	0.55	91.67	1
37	1	NIVA MAJI	812568G	48	5	2	2	2	2	0	2	154	51	21.5	1	8	134	200	7.8	52	0.62	58.3	2
38	2	DULAL CHANDRA MAORA	947434G	40	5	1	2	2	2	0	2	175	69	22.5	3	8	211	300	10	10	0.73	93.3	1
39	1	MST LAILY BEGUM	926686G	48	10	3	1	1	1	0	2	170	60	20.8	1	6	777	550	7.3	400	0.74	60	2
40	1	MANNU K.	650498G	65	18	3	1	2	2	0	2	150	60	26.7	2	4	74	190	6.6	3	0.9	85	1
41	2	GUDLA LAKSHMI TULASI	735885G	48	7	2	1	2	2	0	2	148	72	32.9	3	7	150	210	8.9	100	0.9	78.3	1
42	2	MD REYAZUDDIN	562997G	57	5	2	2	2	2	0	2	159	66	26.1	3	4	229	242	9.4	142	0.67	96.6	1
43	2	MOHAMMED RAFIQUL ISLAM	948498G	52	10	2	1	2	2	0	2	177	72	23	3	2	108	143	6	3	1.05	61.4	1
44	2	DILIP KUMAR ROY	687321G	53	20	3	2	2	2	0	2	164	58	21.6	3	5	110	146	8.5	44	0.94	61.7	1
45	1	PITCHANDI N	881619G	41	8	2	2	2	2	0	2	165	72	26.4	2	8	114	227	6.2	6	0.82	98	1
46	2	MOHAMMED MAHABUB	865412G	52	5	4	2	2	2	0	2	158	65	26	3	8	238	259	12.4	22	0.89	72	1
47	1	ARUMUGAM R.	938501G	56	8	1	2	2	2	0	2	164	68	25.3	1	8	132	216	9.9	42	0.89	135	1
48	1	KONIKA RANI NATH	671446C	57	20	3	1	2	1	0	2	150	48	21.3	1	10	200	399	8.3	400	1	37.5	2
49	1	ROPASHY SENGUPTA	008453H	41	5	2	2	2	2	0	2	154	58	24.5	2	8	290	268	7.4	8	0.57	106	2
50																							

DATA COLLECTION SHEET

I. Study Number :

II. Type of Subject (Case/Control) :

III. Name :

IV. Hospital Number :

V. Age :

VI. Duration of Diabetes :

VII. Diabetic Treatment (None/OHAs/Insulin) :

VIII. Other co morbidities :

Hypertension (yes/no) :

Ischemic Heart Disease (yes/no) :

Dyslipidemia (yes/no) :

IX. Alcohol intake (Units per week) :

X. Thiamine supplements in the last 6 months (Y/N) :

XI. Height (in cm) :

XII. Weight (in Kg) :

XIII. Body Mass Index :

XIV. Type of Amputation (major/minor) :

XV. Neuropathy Disability Score :

XVI. Fasting Blood Sugar (mg/dl) :

XVII. Post-prandial Blood Sugar (mg/dl) :

XVIII. HbA1c (%) :

XIX. Urine Micro-albumin :

XX. Serum Creatinine :

XXI. Erythrocyte Transketolase Activity :

XXII. Thiamine Pyrophosphate effect (%) :

3. **INFORMED CONSENT**

Study Title: *A prospective case control study to compare the thiamine status in people with Type II Diabetes Mellitus undergoing lower limb amputations, and non-neuropathic Type II Diabetics*

Study Number:

Participant's name:

Date of Birth / Age (in years):

I_____

_____, son/daughter of _____

(Please tick boxes)

Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

I understand that I will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

Name:

Signature:

Date:

Name of witness:

Relation to participant:

Date:

Informed Consent - Bengali

অবগতি পত্র (সম্মতিদান)

শিরোনাম: টাইপ ১ ডায়াবেটিস রোগী যাঁদের নিম্নাঙ্গে অস্ত্রোপচার হয়েছে এবং যাঁদের নিম্নাঙ্গে অস্ত্রোপচার হয়নি তাঁদের রক্তে থায়ামিন ভিটামিনের পরিমাণের তুলনামূলক বিচার সংক্রান্ত গবেষনা.

রোগী/রোগিনীর নাম:- _____

জন্ম তারিখ/বয়স:- _____

আমি, _____, _____

পুত্র/কন্যা এতদ্দ্বারা জানাইতেছি যে,

১) আমি _____ তারিখে লিখিত অবগতি পত্র পড়েছি, গবেষনা সম্বন্ধে জেনেছি এবং এই বিষয়ে প্রশ্ন করার পূর্ন সুযোগ পেয়েছি. [ ]

২) আমি এই বিষয়ে অবগত যে আমি এই গবেষনায় সম্পূর্ন স্বেচ্ছায় যোগদান করছি এবং যে কোন মুহূর্তে এই গবেষনা থেকে নিজেকে অপসৃত করতে পারি কোন কারন দর্শন বিনা, এর ফলে আমার কোন আইনত বা চিকিৎসা সংক্রান্ত বিষয়ে প্রভাব পরবেনা. [ ]

৩) আমি জানি যে গবেষক, এথিকস্ কমিটি এবং কর্তব্যক্তিরা আমার অনুমতি বিনা আমার চিকিৎসা-সংক্রান্ত নথি দেখতে পারেন; এই গবেষনা এবং ভবিষ্যত গবেষনার জন্য, আমি যদি এই গবেষনা থেকে নিজেকে অপসৃত করি, সেক্ষেত্রেও। আমি এ বিষয়ে পূর্ন সম্মতিদান করছি। তবে, আমি জানি যে আমার পরিচয় অথবা কোন তথ্যজ্ঞাপূর্ন নথি কোন তৃতীয় ব্যক্তির কাছে প্রকাশিত হবেনা. [ ]

৪) আমি এই গবেষনা লব্ধ সমস্ত তথ্যের পূর্ন-ব্যবহারে সম্মতিদান করছি, কেবলমাত্র বৈজ্ঞানিক প্রকাশের. [ ]

৪) আমি এই গবেষনায় যোগদান করতে সম্মতি. [ ]

১) স্বাক্ষর (অথবা বৃদ্ধাঙ্গুষ্ঠের ছাপ) রোগী/রোগীর আইনত কর্তা/কর্ত্রীর :-

তারিখ :- ___/___/___

স্বাক্ষরকর্তার নাম : _____

২) পরেক্ষকের স্বাক্ষর :-

তারিখ :- ___/___/___

পরেক্ষকের নাম :- অঃ মিথুন রায়

৩) স্বাক্ষীর স্বাক্ষর (অথবা বৃদ্ধাঙ্গুষ্ঠের ছাপ) :-

তারিখ :- ___/___/___

স্বাক্ষীর নাম ও ঠিকানা :-

Informed Consent - Hindi

पैर विच्छेदन और बिना पैर विच्छेदन किये मधुमेह के रोगियों में Thiamine स्थिति की तुलना : एक संभावित रोगी निरोगी अध्ययन

रोगी का नाम :- _____

जन्म तिथी / आयु :- _____

अध्ययन क्रं :- _____

(विषय)

1) मैं इस बात की पुष्टि करता हू कि मैंने उपरोक्त अध्ययन के लिए _____ दिनांकित सूचना पत्रक पढा है, समझा है और सवाल पूछने का अवसर मिला है। [ ]

2) मैं समझता हू कि अध्ययन में मेरी भागीदारी स्वेच्छीक है और मै किसी भी समय नाम वापस ले सकता हूँ, कारण बताये बिना, अपनी चिकित्सा देखभाल प्रभावित किये बिना। [ ]

3) अध्ययन के प्रायोजक, प्रायोजक के और से काम कर रहे अन्य लोगों, आचार समिती और नियामक अधिकारियों को मेरे स्वास्थ्य रिकॉर्ड देखने के लिए मेरी अनुमती की जरूरत नही होगी, हलांकी मेरी पहचान तिसरे पक्ष को प्रकाशित नही कि जायेगी, इसके लिए सहमत हूँ। [ ]

4) मैं इस अध्ययन के डेटा का इस्तमाल केवल वैज्ञानिक उद्देश्य के लिए है इसकी सहमती प्रदान करता हूँ। [ ]

5) मैं इस अध्ययन में भाग लेने के लिए सहमत हूँ। [ ]

हस्ताक्षर (या अंगूठे का निशान) विषय / कानूनी प्रतिनिधी

_____

दिनांक : ___ / ___ / ___

हस्ताक्षरकर्ता का नाम : _____

अन्वेषक के हस्ताक्षर : _____

दिनांक : ___ / ___ / ___

अन्वेषक का नाम : _____

गवाह के हस्ताक्षर (या अंगूठे का निशान) :

_____

दिनांक : ___ / ___ / ___

गवाह का नाम एवं पता : _____

_____

Informed consent-Tamil

இரண்டாம் நிலை சர்க்கரை நோயின் காரணமாக காலின் அடிபகுதியை நீக்கும் அறுவை சிகிச்சையின் பொழுது தையமீனின் அளவை கருத்தில் கொள்ளும் ஆய்வு.

அடையாள எண் :

பங்குபெறுபவர் பெயர் :

பிறந்த தேதி/வயது :

நான் _____ கலந்து கொள்ள _____

[அடைப்புக்குள் தேர்ந்தெடுக்கவும்] தெரிவிப்பது யாதெனில்,

1. அடையாள குறித்த முகவரி அனைத்தையும் நான் __/__/____ தேதியன்று படித்து புரிந்துகொண்டேன் என்பதையும், கேள்வி எழுப்ப வாய்ப்பளிக்கப்பட்டது என்பதையும் புரிந்துகொண்டேன் என உறுதிசெய்கிறேன். [ ]

2. தானாக முன்வந்து அடையாள பங்கெடுக்கிறேன் என்பதையும், இந்த அடையாள இருந்து எந்த நேரத்திலும் விலகிக்கொள்ள முடியும் என்பதையும் புரிந்துகொண்டேன். மேலும் எனது மற்ற மருத்துவ சிகிச்சை முறைகள் மற்றும் சட்ட உரிமைகள் யாவும் பாதிக்கப்படாது என்பதையும் அறிந்துகொண்டேன்.

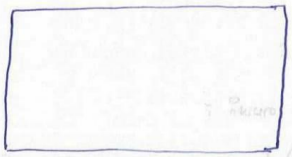
3. அடையாள செய்யும் மருத்துவர், நிறுவன குழுவினர் மற்றும் கட்டுப்பாடு அதிகாரிகள் ஆகிய யாவரும் எனது அனுமதி பெறாமலேயே எனது மருத்துவ பதிவேடுகளை பார்க்கலாம் அனுமதிக்கிறேன். அதே சமயம் இந்த முகவரி தனி வேறு தனிப்பட்ட நபருக்கோ, நிறுவனத்திற்கோ பகிரப்படாமல் என்பதையும் அறிவேன்.

4. மேலும் முகவரி மற்றும் முடிவுகள் அடைய உபயோகம் செய்ய கருத்து பயன்படுத்த ஒத்துக்கொள்கிறேன்.

5. மேற்கண்ட அடையாள பங்குபெற ஒப்புக்கொள்கிறேன்.

1. கையெழுத்தம் (or) வாரிசுதாரர் கையெழுத்தம் : _____

தேதி : __/__/____



[இடது கை பெருவிரல் ரேகை]

ரேகை வைப்பவரின் பெயர் : _____

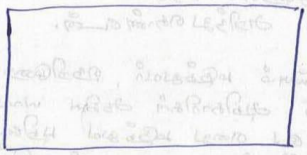
2. அரசு மருத்துவர் கையொப்பம் : _____

தேதி : __/__/____

அரசு மருத்துவர் பெயர் : DR. MITHUN RAAM.

3. சார்பதிவாளர் கையெழுத்தம் _____

தேதி : __/__/____



[இடது கை பெருவிரல் ரேகை]

ரேகை வைப்பவரின் பெயர் : _____

முகவரி :

Informed consent - Telugu

మరియు తక్కువ తీవ్రత అంగచ్ఛేదం లేకుండా టైప్ II మధుమేహం లో థియామిన్ స్థితి యొక్క పోలిక: భావి కేస్ కంట్రోల్ అధ్యయనం

పరిశోధన సంఖ్య:
పాల్గొను వారి పేరు:
పుట్టిన తేది / వయస్సు (సంవత్సరములలో):

నేను _____,
శ్రీ / శ్రీమతి _____ వారి కొడుకు / కూతురును చెప్పునదేమనగా

(i) ఈ పరిశోధనకై రాయబడిని రోగి సమాచార పత్రము లేది _____ బాగా చదివి అర్థము చేసికొని, ప్రశ్నలు అడుగుటకు అవకాశము ఉండెనని నిర్ధారిస్తున్నాను [ ]

(ii) ఈ పరిశోధనలో పాల్గొనడం నాకు ఇష్టం అనియు మరియు నేను ఎప్పుడైన ఏ కారణము చెప్పకుండా నా యొక్క హక్కులకు భంగము కలుగకుండా ఈ పరిశోధన నుండి స్వేచ్ఛగా తప్పుకోవచ్చు అని అర్థంచేసుకున్నాను [ ]

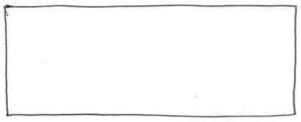
(iii) పరిశోధన కొఱకు, ఎతిక్స్ కమిటి మరియు రెగ్యులేటరీ అథారిటికొనే నా యొక్క హెల్త్ రికార్డును చుడడానికి ఇష్టపడి చేస్తున్న పరిశోధన సంబంధంగా మరియు ఇక ముందు దీనికి సంబందించి చేయబోవు పరిశోధనలలో నేను ప్రియతో గుమయములలో విడిచి పెట్టినను, నా యొక్క అనుమతి అవసరములేకుని చాగా అర్థము చేసుకొన్నాను. నా యొక్క సొంతవివరములు మూడవ మనిషికి చెప్పుటలోనైనను మరియు ప్రచురించుటలోనూ బయటపెట్టరని అర్థంచేసికున్నాను. [ ]

(iv) ఈ పరిశోధన వలన వచ్చిన ఫలితాలను లేకు వేటిలు ఉపయోగించుటకు నేను అభ్యంతరపెట్టను. కానీ వాటిని కేవలము సైనే టిఫిక్ ప్రయోజనములకు వాడుతారని అంగీకరిస్తున్నాను [ ]

(v) నేను పైనున్న పరిశోధనలో పాల్గొనేందుకు అంగీకరిస్తున్నాను. [ ]

1. సంతకము / వేలి ముద్ర (పాల్గొనువారిది లేక రోగి యొక్క సంబంధపువారి)

తేది: _____ / _____ / _____



సంతకము చేసిన వారి పేరు: _____

2. ప్రశ్నలు అడిగిన వారి సంతకము:- _____

తేది: _____ / _____ / _____

పరిశోధన ప్రశ్నలు అడిగినవారు: డా॥ మిథునే రాజు.

3. సాక్షి సంతకము:- _____

తేది: _____ / _____ / _____

పేరు మరియు చిరునామా (సాక్షి యొక్క) :-

4**. Information sheet**

You are being requested to participate in a study to see if the levels of thiamine, a vitamin in your diet correlate with type II diabetes. A common complication of diabetes is nerve damage in the legs and feet which eventually puts you at risk of ulcer formation and possible amputation. Thiamine is a vitamin present in your diet and its deficiency is known to cause nerve damage as well. My study aims to seek a relation between nerve damage in diabetes and the thiamine status of your body. We hope to include about 80 people from this hospital in this study.

What does Thiamine do?

It is known that thiamine is an important part of digestion of the food we eat as well as functioning of our nervous system. There are certain factors which affect the levels of this vitamin in our body which include prolonged intake of alcohol or severe kidney damage. This decrease in thiamine affects nerves and their repair.

What is the relation between thiamine and diabetes?

We have observed that thiamine supplementation helps in the healing of ulcers in animals. We have also seen reduced thiamine levels in diabetic patients with kidney damage. Therefore we wish to see if there is a change in thiamine levels among people who have undergone an amputation of the lower limb due to diabetes and compare them with people who have diabetes but have no nerve damage or amputation.

If you take part what will you have to do?

If you agree to participate in this study, you will be asked a few questions about your age, duration of diabetes and the medications that you are using for diabetes and your height and weight will be measured. We will also be checking your feet for signs of nerve damage. We will also be collecting a single blood sample using standard precautions, to measure the thiamine levels. We will also be collecting information regarding some blood tests previously performed in this hospital, from the medical records system.

All other treatments that you are already on will be continued and your regular treatment will not be changed during this study. No additional procedures or blood tests will be conducted routinely for this study.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

Will you have to pay for the blood test?

The blood test taken from you will be performed free of cost for the purpose of this study.

Any other treatment that you usually take will continue but the usual arrangements that you have with the hospital will decide how much you pay for this.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr. Binoy Abraham, (tel: 0416 2282082/ +91 9994494055) or email: binoy@cmcvellore.ac.in/ docbinoy88@gmail.com

Patient Information sheet - Bengali

অবগতি পত্র

ক্রিশ্চিয়ান মেডিক্যাল কলেজ, ভেলোর
জেনারেল সার্জারি বিভাগ

শীর্ষক: টাইপ টু ডায়াবেটিস রোগী যাঁদের নিম্নাঙ্গ অস্ত্রোপচার হয়েছে এবং যাঁদের নিম্নাঙ্গ অস্ত্রোপচার হয়নি তাঁদের রক্তে থায়ামিন ভিটামিনের পরিমাণের তুলনামূলক বিচার সংক্রান্ত গবেষনা.

আপনাকে এই গবেষনায় (যা আপনার দৈনিক খাবারে উপস্থিত এক ভিটামিন— থায়ামিন 'এর মাত্রা আপনার ডায়াবেটিস টাইপ টু 'র সাথে সামঞ্জস্য রাখে কিনা সে বিষয়ে পরীক্ষা) যোগদান করতে আমন্ত্রন জানাই, ডায়াবেটিস রোগের একটি ফুফল হল, পায়ের এবং নিম্নাঙ্গের স্নায়ু নষ্ট করে দেওয়া যা কালে কালে ক্ষত সৃষ্টি করে এবং ভবিষ্যতে ডায়াবেটিস রোগীদের অস্ত্রোপচারের সম্মুখীন করে। থায়ামিন হল দৈনিক খাদ্যে উপস্থিত একটি ভিটামিন; এবং ভিটামিনের অনুপস্থিতিও স্নায়ুক্ষিংসের একটি অন্যতম কারন বলে জানা গেছে, আমার এই গবেষনার উদ্দেশ্য আপনার শরীরে থায়ামিনের মাত্রা এবং আপনার ডায়াবেটিস রোগের কোন গূঢ় সম্পর্ক আছে কিনা পরীক্ষা করা। আমরা গড়ে ৮০ জন ডায়াবেটিস রোগী, যাঁরা সিএমসি'র চিকিৎসাধীন, তাঁদের সহযোগিতা আশা করি।

* থায়ামিনের গুনাগুন:-

গবেষনায় জানা গেছে যে থায়ামিন পাচনকার্য এবং স্নায়ুর স্বাভাবিক কার্যাবলীর জন্য অত্যন্ত জরুরী। এটিও দেখা গেছে যে কিডনি নষ্ট হয়ে যাওয়া ডায়াবেটিস রোগীদের থায়ামিনের মাত্রা কম। সেই কারন আমরা দেখতে চাই, ডায়াবেটিস রোগী যাঁদের পা কেটে বাদ দিতে হয়েছে, তাঁদেরও থায়ামিনের মাত্রা কম কিনা, যাঁরা ডায়াবেটিস আক্রান্ত কিন্তু এখনো স্নায়ু অক্ষত রয়েছে তাঁদের তুলনায়।

* আপনি যদি যোগদানে ইচ্ছুক হোন :-

আপনি যদি এই গবেষনায় যোগদান করতে সম্মত হন, তাহলে আপনাকে কিছু প্রাথমিক প্রশ্ন করা হবে (বয়স, কতদিন ডায়াবেটিস আছে এবং আপনি ডায়াবেটিসের জন্য কী-কী ওষুধ খান) এবং আপনার উচ্চতা আর ওজন মাপা হবে। আমরা এর সাথে আপনার পায়ের স্নায়ু ঠিকঠাক কাজ করছে কিনা দেখার জন্য কিছু পরীক্ষা করব, এর পরে ইউনিভার্সাল ক্লিকশন পদ্ধতি মোতাবেক সিরিঞ্জ আমরা আপনার রক্তের

একটি নমুনা সংগ্রহ করব, আপনার থায়ামিনের মাত্রা মাপার জন্যে। এই হাসপাতালে, আপনার আগে যা রক্তপরীক্ষা হয়েছে, আমরা সে সম্বন্ধেও কিছু তথ্য সংগ্রহ করব, এই গবেষনার কারণে আপনার দৈনিক চিকিৎসার কোন ব্যাঘাত ঘটবে না। এই গবেষনার জন্য উপরোক্ত পরীক্ষাগুলি ছাড়া অন্য কোন অতিরিক্ত পরীক্ষাও করা হবেনা।

* এই গবেষনা থেকে অপসৃত হওয়া:-

এই গবেষনায় আপনার যোগদান সম্পূর্ন স্বেচ্ছায় এবং আপনি স্বেচ্ছায় এই গবেষনা থেকে নিজেকে অপসৃত করতে পারেন। আপনার এই কাজ, আপনার দৈনিক চিকিৎসার উপর কোন প্রভাব ফেলবেনা।

* এই গবেষনা সংক্রান্ত দুর্ঘটনার ক্ষেত্রে:-

আমরা এই গবেষনার ফলে আপনার কোন শারীরিক বা মানষিক সমস্যার আশঙ্কা করিনা তবু যদি অনিচ্ছাকৃত কোন দুর্ঘটনা ঘটে এই গবেষনার ফলে, তাহলে আপনাকে সেই সমস্যাটির জন্য বিনামূল্যে চিকিৎসা করা হবে। কিন্তু আমরা অতিরিক্ত কোন আর্থিক ক্ষতিপূরন দিতে অপারগ।

* রক্তপরীক্ষার মূল্য:-

এই গবেষনার জন্য সংগৃহীত রক্তের পরীক্ষা বিনামূল্যে করা হবে।
এ ছাড়া আপনার দৈনিক চিকিৎসার ব্যয় আপনাকে হাসপাতালের কর্তৃপক্ষের আয়োজন অনুযায়ী নিজেকে বহন করতে হবে।

* গোপনীয়তা:-

এই গবেষনায় প্রাপ্ত ফলাফল কোন বৈজ্ঞানিক বা চিকিৎসাবিজ্ঞানের পত্রিকায় প্রকাশিত হবে কিন্তু কোথাও আপনার নাম বা পরিচয় প্রকাশিত হবে না। তবে আপনি এই গবেষনায় যোগদান করলে ভবিষ্যতে আপনার অতিরিক্ত অনুমতি ছাড়াই আপনার চিকিৎসাসংক্রান্ত তথ্য গবেষকদল দেখতে পারেন।

বিশদে জানতে যোগাযোগ করুন:-

ডাঃ বিনয় অ্যাব্রাহাম
ফোন:- ০৪৪৬২২৮২০২৮/+৯১ ৯৯৪৪৯৪০৫৫
ইমেল:- binoy@cmcvellore.ac.in / docbinoy88@gmail.com

Patient Information sheet - Hindi

रोगी सूचना शीट

क्रिश्चियन मेडिकल कॉलेज, वेल्लोर

जनरल सर्जरी विभाग

पैर विच्छेदन और बिना पैर विच्छेदन किये मधुमेह के रोगियों में Thiamine स्थिति की तुलना : एक संभावित रोगी निरोगी अध्ययन

आपसे ये अनुरोध किया जा रहा है इस अध्ययन में हिस्सा लेने केलिए जो thiamine के स्तर को मधुमेह के साथ संबंध स्थापित करता है | मधुमेह की एक आम समस्या पैरों में तंत्रिका क्षति है जो आपको अंततः अल्सर गठन के जोखिम में डालता है, जो विच्छेदन का कारण बन सकता है | Thiamine एक विटामिन है जो अपने आहार में मौजूद है, और इसकी कमी से तंत्रिका क्षति हो सकती है | मेरे अध्ययन का उद्देश्य मधुमेह और Thiamine के स्तर के बीच एक संबंध की तलाश करना है | हमें इस अध्ययन में इस अस्पताल से लगभग 50 लोगों को शामिल करने की उम्मीद है।

Thiamine क्या करता है?

Thiamine हमारे तंत्रिका प्रणाली के कामकाज और खाने के पाचन का एक महत्वपूर्ण हिस्सा है | कुछ कारक है जो हमारे शरीर में Thiamine के लेवल को प्रभावित करते हैं जैसे, कि शराब का लंबे समय तक सेवन या गुर्दे की गंभीर क्षति | इस Thiamine की कमी से नसों और नसों के मरम्मत में प्रभाव पड़ता है |

Thiamine और मधुमेह के बीच क्या संबंध है?

हमने देखा है कि, Thiamine देने पर, जानवरों के पैरों के अल्सर के उपचार में सुधार आता है | हमने यह भी देखा है कि मधुमेह के रोगी जिनको गुर्दे की क्षति है , उनके Thiamine के लेवल कम होते हैं | इसलिए, हम देखना चाहते हैं, यदि मधुमेह संबंधित तंत्रिका क्षति के कारण पैरों के अंगछेदन हुए रोगियों के Thiamine लेवल, बिना अंगछेदन हुए मधुमेह रोगियों की तुलना में कम होते है या ज्यादा होते हैं |

यदि आप अध्ययन में भाग लेने के लिए सहमत हैं, तो आपको क्या करना होगा?

यदि आप अध्ययन में भाग लेने के लिए सहमत हैं, तो आपको अपनी उम्र, मधुमेह की अवधि, मधुमेह की दवाओं के बारे में कुछ सवाल पूछे जायेंगे | आपका वजन और ऊंचाई मापा जाएगा | आपके पैरों की तंत्रिका क्षति के लिए, जाँच

की जाएगी | हम Thiamine के स्तर को मापने के लिए, मानक सावधानियों का उपयोग करके ,एक खून का नमूना आपसे एकत्रित करेंगे | हम अस्पताल के मेडिकल रिकॉर्ड सिस्टम से, मधुमेह संबंधित आपके कुछ रक्त परीक्षणों के बारे में जानकारी एकत्रित करेंगे | इस अध्ययन के लिए, कोई अतिरिक्त प्रक्रिया या रक्त परीक्षण नियमित तौर पर नहीं किया जाएगा।

क्या आप अध्ययन शुरू होने के बाद, इस अध्ययन से पीछे हट सकते हैं?

इस अध्ययन में आपकी भागीदारी पूरी तरह स्वैच्छिक है और आप भी इस अध्ययन में भाग लेने के लिए अनुमति वापस लेने का फैसला करने के लिए स्वतंत्र हैं। यदि आप ऐसा करते हैं, तो यह किसी भी तरह से इस अस्पताल में आपके सामान्य उपचार को प्रभावित नहीं करेगा।

क्या शुरू होता है के बाद आप इस अध्ययन से पीछे हट सकते हैं?

इस अध्ययन में आपकी भागीदारी पूरी तरह स्वैच्छिक है और आप भी इस अध्ययन में भाग लेने के लिए अनुमति वापस लेने का फैसला करने के लिए स्वतंत्र हैं। यदि आप ऐसा करते हैं, तो यह किसी भी तरह से इस अस्पताल में अपने सामान्य उपचार को प्रभावित नहीं करेगा।

यदि आप एक अध्ययन से संबंधित चोट विकसित है, तो क्या होगा ?

हमें किसी भी अध्ययन से संबंधित चोट की उम्मीद नहीं है, लेकिन यदि आप किसी भी दुष्प्रभाव या समस्याओं का विकास करते हैं, तो आपका इलाज नि: शुल्क किया जाएगा | हम हालांकि, किसी भी मौद्रिक मुआवजा प्रदान करने में असमर्थ हैं।

क्या आपको इस रक्त परीक्षण का भुगतान करना होगा?

अध्ययन के उद्देश्य के लिए, यह रक्त परीक्षण नि: शुल्क किया जाएगा | आपका सामान्य उपचार जारी रहेगा जिसका भुगतान अस्पताल तय करेगा |

क्या आपकी व्यक्तिगत जानकारी को गोपनीय रखा जाएगा?

इस अध्ययन का परिणाम एक मेडिकल जर्नल में प्रकाशित किया जाएगा, लेकिन आपकी किसी भी प्रकाशन या परिणामों की प्रस्तुति, में पहचान नहीं की जाएगी. हालांकि, आपके चिकित्सा नोटों की समीक्षा, अध्ययन के साथ जुड़े लोगों द्वारा की जा सकती है आपके अतिरिक्त अनुमति के बिना, अगर इस अध्ययन में भाग लेने के लिए आप सहमत हैं |

यदि आपको कोई शक या प्रश्न है, कृपया पूछें **डॉ बिनॉय अब्राहम, (**0416 2282082 / +91 9994494055 **टेल), या ईमेल:** binoy@cmcvellore.ac.in/ docbinoy88@gmail.com

Patient information sheet - Tamil

கிருத்துவ மருத்துவ கல்லூரி, வேலூர்
பொது அறுவை சிகிச்சைப் பிரிவு – 1

இரண்டாம் நிலை சர்க்கரை நோயின் காரணமாக காலின் அடிபகுதியை நீக்கும் அறுவை சிகிச்சையின் பொழுது தையமீனின் அளவை கருத்தில் கொள்ளும் ஆய்வு.

இரண்டாம் நிலை சர்க்கரை நோயில் தையமீன் என்னும் வைட்டமினின் அளவை கண்டறியும் ஆய்வில் தாங்கள் பங்கேற்க அழைக்கப்பட்டு இருக்கிறீர்கள். இரண்டாம் நிலை சர்க்கரை நோயில் நரம்பு சேதாரமானது ஒரு பொதுவான பிரச்சனை ஆகும். இந்த நரம்பு சேதாரமானது இறுதியில் சீழ்புண்ணாக மாற வாய்ப்பு உள்ளது மற்றும் இந்த நிலையானது காலை நீக்கும் அளவிற்கு கொண்டு செல்லும். தையமீன் என்பது ஒரு வகையான வைட்டமின் ஆகும். இந்த வைட்டமின் ஆனது நாம் உண்ணும் உணவிலேயே உள்ளது. இந்த வைட்டமின் குறைபாடு காரணமாக நரம்பில் சீழ்புண் உருவாகிறது. என்னுடைய இந்த ஆய்வானது தையமினின் குறைவால் ஏற்படும் குறைபாடு மற்றும் இரண்டாம் நிலை சர்க்கரை நோயினால் உங்களது உடலில் ஏற்படும் பாதிப்புகளையும் கண்டறிய பயன்படும். இந்த ஆய்வில் நாங்கள் சுமார் 80 நோயாளிகளை பரிசோதனைக்கு உட்படுத்த திட்டமிடப்பட்டுள்ளது.

தையமினின் வேலைகள் என்ன?

தையமின் என்னும் வைட்டமின் ஆனது உணவு செரிமானத்திலும் மற்றும் நரம்பு மண்டல செயல்பாட்டிலும் முக்கிய பங்கு வகிக்கிறது. இந்த வைட்டமின் குறைபாடு ஏற்படுவதற்கு சில காரணிகள் உள்ளன அவை மது அருந்துதல் மற்றும் சிறுநீரக குறைபாடுமே ஆகும். இந்த காரணிகளானது தையமின் அளவை குறைத்து நரம்புகளை பாதிப்புக்குள்ளாக்கிறது மற்றும் அறுவை சிகிச்சை செய்யும் அளவிற்கு கொண்டு செல்கிறது.

தைமினுக்கும் சர்க்கரை நோய்க்கும் உள்ள சம்பந்தம் என்ன?

தையமினை கூடுதலாக சேர்ப்பதன் மூலம் விலங்குகளின் காலில் வரும் புண் குணமடைவதை பரிசோதனையின் மூலம் கண்டறிந்தோம். இது மட்டுமல்லாமல் இரண்டாம் நிலை புற்று நோயாளிகளில் தையமின் குறைபாடு அதிகமாக இருப்பதை காணலாம். ஆதலால் நாங்கள் இந்த வைட்டமினை கூடுதலாக சேர்ப்பதன் மூலம் சர்க்கரை குறைபாடு உள்ள மற்றும் அதன் காரணமாக அறுவை சிகிச்சை செய்து கால் நீக்கபட்ட நோயாளிகளையும் சர்க்கரை நோய் உள்ள ஆனால் நரம்பு பாதிப்புக்கு உட்படாத நோயாளிகளையும் ஆய்வு செய்ய உள்ளோம்.

இந்த ஆய்வில் பங்கேற்க நான் என்ன செய்ய வேண்டும்?

இந்த ஆய்வில் நீங்கள் பங்கேற்பதாக இருந்தால் நீங்கள் உங்கள் வயது சர்க்கரை நோய் எவ்வளவு காலமாக இருக்கிறது மற்றும் அதற்காக நீங்கள் உட்கொள்ளும் மருந்துகளின் அளவுகளை பற்றி பதலளிக்க வேண்டியது இருக்கும். உங்களது உடல் எடை மற்றும் உயரம் கணக்கிடப்படும். அதுமட்டுமல்லாது நாங்கள் உங்களது பாதங்களை பரிசோதித்து நரம்பு பாதிப்புக்கான எதாவது அறிகுறி இருக்கிறதா என்பதனையும் பார்ப்போம். நாங்கள் உங்களிடமிருந்து சிறிது இரத்தத்தை பரிசோதனைக்கு எடுத்து அதில் தயமினின் அளவை சரிபார்ப்போம். இந்த ரத்த பரிசோதனையானது முன்னெச்சரிக்கையுடன் மேற்க்கொள்ளப்படும். அது மட்டுமல்லாது இதற்கு முன்பாக உங்களுக்கு இந்த மருத்துவமனையில் எடுக்கப்பட்ட இரத்த பரிசோதனையின் தகவல்களையும் பரிசீலனை செய்யப்படும்.

இந்த ஆய்வின்போது நீங்கள் மேற்க்கொள்ளும் மற்ற சிகிச்சைகள் எந்தவித பாதிப்புமின்றி தொடரும். எந்தவிதமான கூடுதல் பரிசோதனைகளும் இந்த ஆய்விற்காக செய்யப்படமாட்டாது.

நீங்கள் இந்த ஆய்விலிருந்து வெளியேற முடியுமா?

இந்த ஆய்வில் உங்கள் பங்கேற்பானது முழுவதும் தன்னார்வமானதே மற்றும் நீங்கள் எந்நேரமும் இந்த ஆய்விலிருந்து வெளியேறலாம். அப்படி வெளியேறினால் உங்களது மருத்துவ சிகிச்சையானது எந்த விதத்திலும் பாதிக்கப்படாது.

இந்த ஆய்வில் பங்கேற்கும்பொழுது இந்த ஆய்வு சம்பந்தமான ஏதேனும் உடல் காயம் ஏற்ப்பட்டால் என்னவாகும்?

தங்களுக்கு எந்தவிதமான உடல் காயமும் ஏற்படாது. ஆனால் இந்த ஆய்வில் பங்குகொள்வதன் மூலம் ஏதேனும் பக்க விளைவுகள் ஏற்படுமாயின் தங்களுக்கு இலவசமாக சிகிச்சை அளிக்கப்படும். ஆனால் எங்களால் தங்களுக்கு எந்தவிதமான பண உதவியும் செய்ய இயலாது.

நான் இந்த பரிசோதனை செய்ய கட்டணம் செலுத்த வேண்டி வருமா?

தங்களுக்கு செய்யப்படும் இரத்த பரிசோதனையானது இலவசமாகவே செய்யப்படும். எந்தவிதமான கட்டணமும் வசூலிக்கப்படமாட்டாது.

நீங்கள் இந்த மருத்துவமனையில் மேற்க்கொள்ளும் மற்ற சிகிச்சைகளுக்கு தாங்கள் எவ்வாறு கட்டணம் செலுத்தி வந்தீர்களோ அதே போன்று கட்டணம் வசூலிக்கப்படும்.

எனது தனிப்பட்ட தகவல்கள் இரகசியமாக வைக்கப்படுமா?

இந்த ஆய்வின் முடிவானது மருத்துவ பத்திரிக்கைளில் வெளியிடப்படும். ஆனால் உங்களது பெயரோ அல்லது மற்ற எந்த தனிப்பட்ட தவகல்களோ வெளியிடப்படமாட்டாது. ஆனால் நாங்கள் மட்டுமல்லாமல் இந்த ஆய்வில் உள்ள மற்ற மருத்துவர்கள் உங்களது மருத்துவ தகவல்களை ஆய்வாளர்கள் தணிக்கை செய்வார்கள். இதற்காக உங்களிடமிருந்து தனியான ஒப்புதல் பெறப்படமாட்டாது. இவை அனைத்தும் நீங்கள் ஒப்புதல் அளித்த பின்னரே ஆரம்பிக்கப்படும்.

உங்களுக்கு ஏதேனும் கேள்விகள் இருப்பின் தயவுசெய்து கீழ்கண்ட விலாசத்தில் தொடர்பு கொள்ளவும்

டாக்டர் பினாய் ஏப்ரகாம்
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Patient information sheet - Telugu

పేషంట్ ఇన్ఫర్మేషన్ షీట్

క్రిస్టియన్ మెడికల్ కాలేజ్, వెల్లూరు
జనరల్ సర్జరీ శాఖ

మరియు తక్కువ తీవ్రత అంగచ్ఛేదం లేకుండా టైప్ II మధుమేహం లో థియామిన్ స్థితి యొక్క పోలిక: భావి కేస్ కంట్రోల్ అధ్యయనం

ఆహారంలో థియామిన్ విటమిన్ స్థాయిలు, టైప్ II మధుమేహం తో కలిసి ఉంటే చూడటానికి ఒక అధ్యయనంలో పాల్గొనేందుకు ఆహ్వానిస్తున్నాము . మధుమేహం ఒక సాధారణ సమస్య ఇది కాళ్ళు మరియు పాదాల నరాలు దెబ్బ ఉంది చివరికి పుండు ఏర్పడటానికి మరియు విచ్ఛేదనం ప్రమాదం ఉంచుతుంది . థియామిన్ విటమిన్ మీ ఆహారంలో దాని లోపం అలాగే నరాల నష్టం కారణం అంటారు. నా అధ్యయనం నరాల నష్టం మధుమేహం మరియు మీ శరీరం యొక్క థియామిన్ స్థితి మధ్య ఒక బంధం ఉంటుంది లక్ష్యం. మేము ఈ అధ్యయనంలో ఈ ఆసుపత్రి నుండి 80 పేషెంట్ ఆశిస్తున్నాము.

థయమైస్ ఏమి చేస్తుంది?

ఇది థియామిన్ మా నాడీ వ్యవస్థ యొక్క ఒక ముఖ్యమైన విటమిన్ తినడానికి ఆహార జీర్ణక్రియ భాగంగా అలాగే పనితీరును అని అంటారు. మద్యం లేదా తీవ్రమైన మూత్రపిండాల నష్టం దీర్ఘకాల వాడకం వలన వీటిలో మా శరీరం లో ఈ విటమిన్ స్థాయిలను ప్రభావితం కొన్ని కారకాలు ఉన్నాయి. థియామిన్ తగ్గిన నరములు మరియు వారి మరమ్మత్తు ప్రభావితం చేస్తుంది.

థియామిస్ మరియు మధుమేహం మధ్య సంబంధం ఏమిటి?

మేము థియామిన్ సప్లిమెంటేషన్ జంతువులలో పాదం పూతల యొక్క వైద్యం లో సహాయపడుతుంది గమనించాము. మూత్రపిండాల నష్టం డయాబెటిక్ రోగుల్లో తగ్గిన థియామిన్ స్థాయిలు గమనించాము. అందువలన మధుమేహం లో లింబ్ విచ్ఛేదనం జరిగాయని, మధుమేహం కలిగి, ఏ నరాల నష్టం లేదా విచ్ఛేదనం కలిగిన వ్యక్తులతో మధ్య థియామిన్ స్థితి యొక్క పోలిక .

మీరు పాల్గొంటే మీకు ఏమి చేయవలసి ఉంటుంది?

మీరు ఈ అధ్యయనంలో పాల్గొనేందుకు ఆమోదిస్తే, మీరు కొన్ని ప్రశ్నలు మీ వయస్సు గురించి, మధుమేహం యొక్క వ్యవధి మరియు మీరు మధుమేహం కోసం ఉపయోగిస్తున మందులు అడగబడతారు మరియు మీ

ఎత్తు మరియు బరువు కొలుస్తారు చేయబడుతుంది . మేము కూడా నరాల నష్టం సంకేతాలను మీ అడుగుల తనిఖీ చేయబడుతుంది. మేము కూడా థియామిన్ స్థాయిలను లెక్కించడానికి, ప్రామాణిక జాగ్రత్తలను ఉపయోగించి ఒక రక్త నమూనా సేకరించడం. మేము కూడా వైద్య రికార్డుల వ్యవస్థ నుండి, గతంలో ఈ ఆసుపత్రిలో నిర్వహించిన కొన్ని రక్త పరీక్షలు సంబంధించిన సమాచారం సేకరించడం.
మీరు ఇప్పటికే అన్ని ఇతర చికిత్సలు కొనసాగింది చేయబడుతుంది మరియు మీ రెగ్యులర్ చికిత్స ఈ అధ్యయన కాలంలో మారవు. అదనపు విధానాలు లేదా రక్త పరీక్షలు ఈ అధ్యయనం కోసం మామూలుగా నిర్వహించిన ఉంటుంది.

ఇది మొదలవుతుంది తర్వాత మీరు ఈ అధ్యయనం నుండి వెనక్కి తీసుకోవచ్చు?

ఈ అధ్యయనంలో మీ పాల్గొనడం పూర్తిగా స్వచ్ఛంద మరియు మీరు కూడా ఈ అధ్యయనంలో పాల్గొనేందుకు అనుమతి స్వేచ్ఛగా నిర్ణయించుకుంటారు ఉపసంహరించుకోవాలనికుడా స్వేచ్ఛగా చేయొచ్చు . మీరు ఇలా చేస్తే, ఈ ఆసుపత్రి వద్ద మీ సాధారణ చికిత్స ఏ విధంగాప్రభావితం చేయదు.

మీరు ఏ అధ్యయనం సంబంధిత గాయం అభివృద్ధి చేస్తే ఏమవుతుంది?

ఈ అధ్యయనం మీకు ఏ గాయం చేయదు. మీరు అధ్యయనం కారణంగా ఏ దుష్ప్రభావాలు లేదా సమస్యలు వచ్చిన, మీకు ఎటువంటి ఖర్చు లేకుండా చికిత్స చేయబడుతుంది. అయితే, ఏ ద్రవ్య పరిహారం అందించము.

మీరు రక్త పరీక్ష కోసం చెల్లించవలసి ఉంటుంది?

మీరు నుంచి తీసుకున్న రక్త పరీక్ష ఈ అధ్యయనం యొక్క ఉపయోగం కోసం ఉచితముగా చేయబడుతుంది. మీరు సాధారణంగా పడుతుంది ఏ ఇతర చికిత్స కొనసాగుతుంది కానీ మీరు ఆసుపత్రితో కలిగి సాధారణ ఏర్పాట్లు మీరు చెల్లించాల్సిన ఉంటుంది .

మీ వ్యక్తిగత వివరాలు గోప్యంగా ఉంచబడతాయి?

ఈ అధ్యయనం యొక్క ఫలితాలు వైద్య పత్రికలో ప్రచురించబడుతుంది కానీ ఏ ప్రచురణ లేదా ప్రదర్శన లో పేరు ద్వారా గుర్తించలేరు. అయితే, మీ వైద్య రికార్డు అనుమతి లేకుండా అధ్యయనంతో అనుబంధించబడుతుంది ప్రజలు, సమీక్షించబడవచ్చు.

మీరు ఏవైనా ప్రశ్నలు ఉంటే, డాక్టర్ Binoy అబ్రహం అడగండి (tel: 0416 2282082/ +91 9994494055) or email: binoy@cmcvellore.ac.in/docbinoy88@gmail.com